CASE REPORTS

Treatment of Medullary Carcinoma of the Thyroid with I-131

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We present a patient with radioiodine concentration in pulmonary metastases presumably arising from medullary carcinoma of the thyroid. Transient symptomatic improvement occurred after treatment with a large dose of sodium iodide (I-131). Although radioiodine concentration in medullary carcinoma of the thyroid is rare, the findings in this patient and in other recent reports suggest that an attempt should be made to determine whether a medullary carcinoma concentrates radioiodine. If so, I-131 treatment might be beneficial.

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Medullary carcinoma of the thyroid (MCT) is an unusual form of thyroid carcinoma arising from calcitonin-secreting parafollicular cells in the thyroid gland. These cells are not involved with thyroid hormone synthesis, and therefore treatment with I-131 has not been considered efficacious in the management of MCT. For the most part, surgical extirpation has been thought the only effective means of treatment, and total thyroidectomy has been used because of the multifocal distribution of the disease. Surgery and external radiotherapy have been applied palliatively in advanced cases, but widespread extension and a tendency to early distant metastases result in a rather poor prognosis despite the generally slow rate of tumor growth (*1*).

In recent years there have been several somewhat encouraging reports of treatment of medullary carcinoma of the thyroid with I-131 (*2,3*). Furthermore, there have been a few cases of MCT demonstrating tumor concentration of radioiodine (*3,4*). This communication describes a patient with MCT and pulmonary metastases, presumably also MCT, that concentrated radioiodine. As a result the patient was treated with a large dose of I-131, following which there was temporary symptomatic improvement.

CASE REPORT

A 53-yr-old Latin-American construction foreman first presented in May 1978 with an asymptomatic neck mass that had been increasing in size for the previous 10 mo. Physical examination revealed a hard 5-cm round mass in the left lower anterior triangle of the neck and a 5×9-cm hard mass in the midline above the sternum. Chest radiograph and laboratory findings were unremarkable. Total thyroidectomy and left radical neck dissection were performed for thyroid tumor, and the surgery revealed mediastinal involvement and cervical lymph-node metastases. Microscopy showed the tumor to be a pure medullary carcinoma of the thyroid without any evidence of papillary or follicular elements (Fig. 1). A serum calcitonin level obtained postoperatively was 15,000 pg/ml. Following surgery he was treated with 5600 rad of external radiation to the neck and mediastinum over a two-month period and was maintained on L-thyroxine for hypothyroidism.

In February 1979, fluffy nodular infiltrates were seen on the chest radiograph and were deemed compatible with metastatic tumor. The serum calcitonin level had increased considerably (Table 1). The patient was treated with a series of chemotherapeutic agents, including cis-platinum and doxorubicin hydrochloride, following which further treatment was refused.

He was readmitted to the hospital on April 2, 1980 complaining of productive cough, progressive dyspnea, diarrhea, and 24-pound weight loss. He also noted a blind spot in the right visual field. He was cachectic, cyanotic, and hyperpneic. There were shotty lymph nodes in the left cervical region and a superior scotoma of the right visual field. Visual acuity was 20/400 for the right eye and 20/20 for the left. Funduscopic examination revealed a mottled choroidal mass lesion beneath the macula of the right eye. Chest radiograph showed progression of the infiltrates (Fig. 2), and serum calcitonin concentrations had increased over previous values (Table 1). The patient was treated with fluids, antibiotics, and bronchodilators, with slight symptomatic respiratory improvement, but dyspnea and hyperpnea persisted, and continuous nasal oxygen was required.

Five days after discontinuation of L-thyroxine, 15 mCi of sodium pertechnetate(Tc-99m) was administered to confirm the absence of all thyroidal tissue. Scintigraphy revealed no uptake in the neck, but some was seen in the lung fields at the edge of the image. Accordingly, 1.8 mCi of sodium iodide(I-131) was administered two

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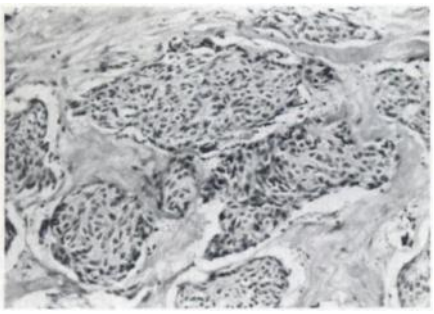

FIG. 1. Photomicrograph of medullary thyroid carcinoma. Note that tumor is pure MCT and nests of tumor cells are imbedded in amyloid stroma. (Microscopic magnification 100X.)

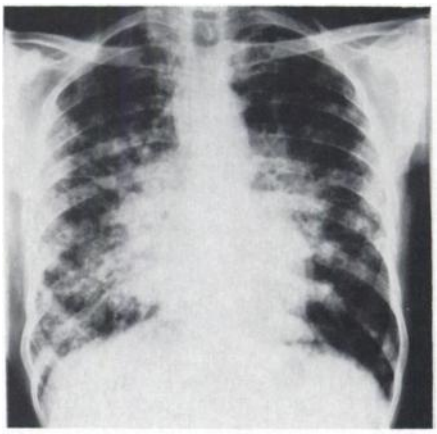

FIG. 2. Chest radiograph showing extensive metastatic infiltrates in both lungs. Compare distribution of radioiodine, in Fig. 3, with distribution of infiltrates in this radiograph.

days later and detailed views of the neck, chest, and whole body were obtained. No activity was noted in the neck or eyes, but both lungs concentrated radioiodine strongly (Fig. 3).

Knowledge of a prior report of medullary carcinoma concentrating radioiodine (*4*) prompted repeat studies six days later, using 5 mCi of sodium iodide(I-131). By 24 hr, the total lung uptake of radioiodine was 12.6%, without attenuation correction. The lung uptake was calculated using computer-integrated total lung counts and total counts from three point sources of iodine-131. The "in air" counts of the standards were corrected for tissue attenuation, resulting in a corrected lung uptake of 31.5% (*5*). Then 1 g of potassium perchlorate was given by mouth, and the uptake of radioiodine in the lungs over the subsequent 90 min was determined at 15-min intervals. There was precipitous washout of the radioactivity from the lungs, indicating absence of organification in the metabolism of radioiodine (Figs. 3 and 4).

We believed that the pulmonary lesions were pure MCT, but a pulmonary biopsy to prove this was ruled out because of the patient's precarious pulmonary status. To eliminate perchlorate and decrease the patient's body burden of iodine, he was given furosemide and was placed on low iodine intake. Six days later, bovine thyrotropin, 10 units daily, was given for three days, and on the third day, 321 mCi of sodium iodide(I-131) was administered by mouth. By this time the serum free thyroxine index had decreased from 10.1 while on thyroxine to 3.4 (normal 4.4–11.2) and the TSH was high (38 μU/ml). Two days after administration of the radioiodine, the patient noted sudden improvement in vision and reported shrinkage of the scotoma. Visual acuity in the right eye improved to 20/50; the left remained at 20/20. At one week after treatment, exercise tolerance had increased significantly, nasal oxygen was not needed and the diarrhea had also improved considerably. The patient was discharged from the hospital two days later on L-thyroxine, tetracycline, aminophyllin, and analgesics.

Following discharge the patient returned to work for 4 mo. He returned to the hospital in early September 1980 complaining of recurrent increasing diarrhea and shortness of breath, weight loss, and weakness. Hematological studies showed no evidence of bone-marrow depression but by radiograph the pulmonary lesions had progressed considerably. He died in mid September 1980; unfortunately, postmortem examination was not obtained.

DOSIMETRY CALCULATIONS

The total urine output after the therapeutic dose of iodine was collected daily. If it is assumed that the ratio of lung to total-body uptake remained at the level determined by the 24-hr lung mea-

TABLE 1. BASAL SERUM CALCITONIN CONCENTRATIONS

Date	Calcitonin concentration (pg/ml)*	Comment
May 1978	15,000	Immediately after surgery
September 1978	5,230	After external radiation
March 1979	61,100	Before chemotherapy
April 1980	250,000	Before I-131 treatment
April 1980	280,000	One week after I-131 treatment
August 1980	235,000	Four months after I-131 treatment

* Normal, less than 50 pg/ml, performed by Bio Science Laboratories, Van Nuys, California (*13*).

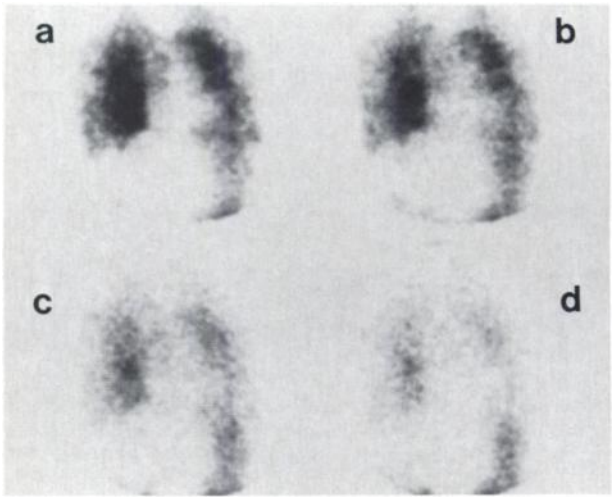

FIG. 3. Potassium perchlorate washout test. Baseline scintigram (a) obtained 24 hr after administration of diagnostic dose of iodine-131 but before $KClO_4$; (b, c, d) lung activities at 30, 60, and 90 min, respectively, after $KClO_4$.

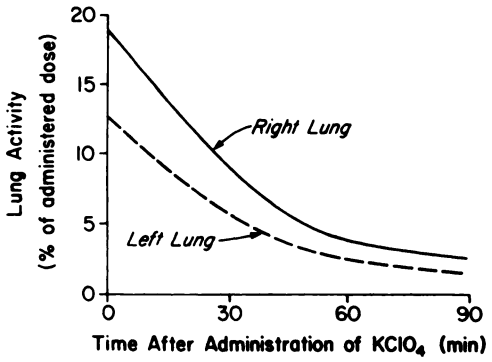

FIG. 4. Washout curves of lung activity derived from potassium perchlorate washout images of Fig. 4. Ordinate shows percentage uptake of radioiodine in each lung, corrected for tissue attenuation.

surements and that removal of radioiodine occurred only by physical decay and excretion in urine, then the total amount of radioiodine retained at the end of each day of treatment can be calculated. Application of linear regression and curve-stripping techniques showed that the retention of radioiodine can be described by a two-compartment exponential model (Fig. 5), whose fast and slow components give biological half-times of 0.63 day and 7.95 days, respectively.

The radiation dose to the patient's lungs was estimated by the method of Loevinger and Berman (*6*). The cumulated activity was calculated by multiplying the zero-time activity of each of the two components of the retention curve (Fig. 5) by the respective average effective lifetime.

$$\tilde{A} = (156{,}000\ \mu\text{Ci})\ (1.44)\left(\frac{0.63 \times 8.1}{0.63 + 8.1}\text{d}\right) + (165{,}000\ \mu\text{Ci})\ (1.44)\left(\frac{7.95 \times 8.1}{7.95 + 8.1}\text{d}\right)$$
$$= 1.086 \times 10^6\ \mu\text{Ci-d} = 2.61 \times 10^7\ \mu\text{Ci-hr}.$$

The absorbed dose S per unit cumulated activity for iodine-131 residing in and irradiating the lungs is

$$4.5 \times 10^{-4}\ \frac{\text{rad}}{\mu\text{Ci-hr}}$$

and for total body (TB) irradiating lungs is (*7*)

$$1.0 \times 10^{-5}\ \frac{\text{rad}}{\mu\text{Ci-hr}}.$$

Therefore,

$$D(\text{lung} \rightarrow \text{lung}) = (\text{lung uptake})\ (\tilde{A})\ [S(\text{lung} \rightarrow \text{lung})]$$
$$= (0.315)\ (2.61 \times 10^7\ \mu\text{Ci-hr})\left(4.5 \times 10^{-4}\ \frac{\text{rad}}{\mu\text{Ci-hr}}\right)$$
$$= 3696\ \text{rad};$$

$$D(\text{TB} \rightarrow \text{lung}) = (\text{TB uptake})\ (\tilde{A})[S(\text{TB} \rightarrow \text{lung})]$$
$$= (0.685)(2.61 \times 10^7\ \mu\text{Ci-hr})\left(1.0 \times 10^{-5}\ \frac{\text{rad}}{\mu\text{Ci-hr}}\right)$$
$$= 179\ \text{rad};$$

$$\text{Total dose to lungs} = D\ (\text{lung} \rightarrow \text{lung}) + D(\text{TB} \rightarrow \text{lung})$$
$$= 3696\ \text{rad} + 179\ \text{rad}$$
$$= 3875\ \text{rad}.$$

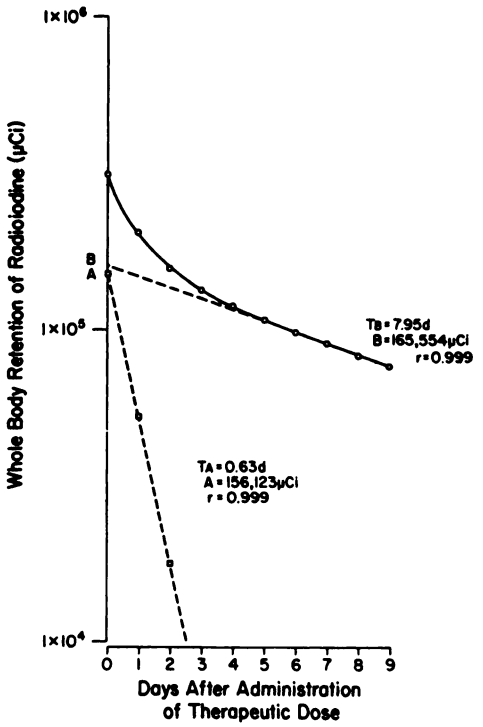

FIG. 5. Whole-body retention of iodine-131 as a function of time after therapeutic dose. Data are corrected for radioactive decay, and indicate a two-compartment model, with rate constants and initial concentrations as shown.

Calculations using the classical method of Johns (*8*) yield a dose of 4180 rad; thus the actual dose delivered to the lungs was approximately 4000 rad.

DISCUSSION

Medullary carcinoma of the thyroid arises from the parafollicular or C cells of the thyroid gland. These cells are derived from neural crest tissue (*9*). In mammals they migrate into the thyroid gland, but in other vertebrates they are anatomically as well as functionally distinct tissues. The parafollicular cells secrete the calcium-regulating hormone calcitonin and are not concerned with the production of thyroid hormones. Medullary carcinomas also secrete calcitonin, and elevated concentrations of this hormone have been used as a tumor marker (*10*). Whereas other biologically active hormones have been shown to be secreted by thyroidal medullary carcinomas, iodine-containing substances are not. Thus, efforts to determine whether medullary carcinoma cells concentrate iodine have in general been unsuccessful (*11,12*). As a result, radioiodine has been used only rarely in the treatment of medullary carcinoma, since conventional wisdom has it that the radioiodine would not localize and irradiate the carcinoma cells (*1*).

There have been rare reports, however, of treatment of medullary carcinoma with radioiodine. Hellman et al. (*2*) took advantage of the presence of normal follicles close to cancerous cells. They demonstrated a diminution in elevated serum calcitonin levels after administration of 150 mCi of I-131 to a 16-yr-old girl with MCT. They calculated that 34,000 rad were delivered to the thyroid bed and suggested that I-131 may be effective therapy in patients with MCT if residual disease is confined to the area near the thyroid bed.

Rasmusson and Hansen also applied I-131 in the treatment of MCT (*3*). In their series, five of six patients treated with I-131 (alone or combined with other therapy) showed significant de-

creases in serum calcitonin and in either tumor size or the diarrhea associated with MCT. One of their patients showed I-131 uptake in bone metastases, but in others there was no localized uptake, and the cause of the improvement was obscure. In any event, they recommended I-131 treatment if other methods failed.

Recently, Parthasarathy et al. (*4*) reported concentration of thallous(Tl-201) chloride, pertechnetate (Tc-99m), and sodium iodide(I-131) in a patient with MCT with regional neck and mediastinal metastases. No evidence was found for the presence of concomitant follicular cancer that might have accounted for the tracer uptake. A perchlorate washout test was markedly positive, indicating little or no organification.

Our patient's pulmonary metastases showed similar iodine trapping without organification. Although necropsy was not obtained, the lung tumors were very probably pure MCT. There are three reasons for this view: (a) In spite of careful search, the thyroid sections showed no evidence of follicular carcinoma; (b) such a component, if present in the lung metastases, would have resisted perchlorate washout; and (c) there was extraordinary output of calcitonin as the pulmonary invasion advanced.

Because of the uptake in the tumor we were able to irradiate it locally, and administered 321 mCi of I-131. The patient promptly began to improve and returned to work within weeks, but we hesitate to ascribe the improvement to the I-131 alone, especially since the serum calcitonin remained high (Table 1). Other factors may have contributed, but there was improvement nonetheless, lasting about 4 mo.

It is clear, at any rate, that one should not assume that medullary carcinoma of the thyroid will not concentrate radioiodine. A rare patient does demonstrate this phenomenon, and this opportunity may be seized to afford treatment with large doses of I-131. Furthermore, favorable effects on the course of MCT appear to have resulted from administration of radioiodine in large therapeutic doses, even to patients who do not show tumor iodine uptake, probably from localization of radiopharmaceutical in adjacent normal thyroid tissue (*2*).

In conclusion, considering the dismal prognosis of patients with metastatic MCT, an attempt should be undertaken to determine whether radioiodine treatment might provide beneficial effects.

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REFERENCES

1. HILL CS, IBANEZ ML, SAMAAN NA, et al: Medullary (solid) carcinoma of the thyroid gland: An analysis of the M. D. Anderson Hospital experience with patients with the tumor, its special features, and its histogenesis. *Medicine* 52:141-171, 1973
2. HELLMAN DE, KARTCHNER M, VAN ANTWERP JD, et al: Radioiodine in the treatment of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 48:451-455, 1979
3. RASMUSSON B, HANSEN HS: Treatment of medullary carcinoma of the thyroid: Value of calcitonin as tumour marker. *Acta Radiol Oncol* 18:521-534, 1979
4. PARTHASARATHY KL, SHIMAOKA K, BAKSHI SP, et al: Radiotracer uptake in medullary carcinoma of the thyroid. *Clin Nucl Med* 5:45-48, 1980
5. MORITA R, LIEBERMAN LM, BEIERWALTES WH, et al: Percent uptake of ^{131}I radioactivity in the adrenal from radioiodinated cholesterol. *J Clin Endocrinol Metab* 34:36-43, 1972
6. LOEVINGER R, BERMAN M: A revised schema calculating the absorbed dose from biologically distributed radionuclides. Medical Internal Radiation Dose (MIRD) Committee Pamphlet No. 1, revised. New York, Society of Nuclear Medicine, 1976
7. SNYDER WS, FORD MR, WARNER GG, et al: "S," Absorbed dose per unit cumulated activity for selected radionuclides and organs. *Medical Internal Radiation Dose (MIRD) Committee Pamphlet No. 11.* New York, Society of Nuclear Medicine, 1975
8. JOHNS HE, CUNNINGHAM JR: *The Physics of Radiology.* Springfield, Illinois, Charles C. Thomas, 1974, pp 564-574
9. POTTS JT JR: Medullary carcinoma of the thyroid and calcitonin. In. *Harrison's Principles of Internal Medicine, Eighth Edition.* Thorn GW, Adams RD, Braunwald E, et al., Eds. New York, McGraw-Hill Book Company, 1977, pp 2026-2027
10. MELVIN KEW, MILLER HH, TASHJIAN AH JR: Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. *New Engl J Med* 285:1115-1120, 1971
11. LJUNGBERG O: Medullary carcinoma of the human thyroid gland. Autoradiographic localization of radioiodine. *Acta Path Microbiol Scand* 68:476-480, 1966
12. DAVIS PW: A review of 17 cases of medullary carcinoma of the thyroid gland. *Proc R Soc Med* 60:743-744, 1967
13. DEFTOS LJ: Immunoassay for human calcitonin. I. Method. *Metabolism* 20:1122-1128, 1971