Radioiodide Uptake and Turnover in a Pseudo-Medullary Thyroid Carcinoma

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A mass in a woman's neck, with no sequestration by Tc-99m imaging, was accompanied by an elevated serum calcitonin on one occasion. Light microscopy of a biopsy was consistent with medullary thyroid carcinoma. Electron microscopy showed secretory granules similar to those found in normal C-cells and in medullary carcinoma of the thyroid. The neck mass (and pulmonary and hepatic metastases likely from the principal mass) concentrated radioiodide (I-131). Subsequent immunoperoxidase examination of the tissues showed them to contain thyroglobulin but not calcitonin. The tumor was thus likely of follicular-cell origin. Reports of radioiodide uptake in medullary thyroid carcinoma may be correct, but each case will have to be re-examined with attention to tissue markers such as thyroglobulin and calcitonin. These markers might more correctly classify the origin of the tumor. The possibilities of cell interconversion and of dual origin are also discussed. Whole-body turnover of radioiodide was quantified as well as that in the pulmonary lesions. Rapid removal of radioactivity was present, suggesting that agents reducing iodide turnover might have therapeutic value in these cases. At five days after radioiodide administration, a biopsy specimen showed that the tumor-to-blood ratio (per gram) was greater than 1.

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There has been recent interest in the use of radioiodide to treat tumors reported as being medullary carcinomas of the thyroid, but the evidence has been conflicting. We present a review of available information (Table 1) and discuss a case that points out the need for definitive histological verification.

CASE REPORT

A woman (age 69 yr), who had been taking thyroid hormones intermittently for two decades, was seen at another hospital because of a mass in the left side of the neck. A [^{99m}Tc]pertechnetate image revealed the thyroid to be functional, whereas the palpable mass was a focal area of decreased activity involving the left lobe. A left lobectomy was performed. Optical microscopy of the nodule was reported as showing a medullary thyroid carcinoma. Of three serum calcitonin determinations performed preoperatively, only one had been slightly elevated (268 pg/ml, against normal upper limit of 100 pg/ml).

She was seen at this center 9 mo later because of an enlarging right neck mass, difficulty in breathing, and intermittent hemoptysis. A chest radiograph revealed nodular densities in the lungs (Fig. 1, top). The right lower neck lesion was biopsied and examined by both light and electron microscopy. The findings matched those of the initial left-side nodule. The tumor resembled medullary thyroid carcinoma.

Light microscopy. The mass was predominantly composed of solid irregular islands of tumor cells separated by a hyaline stroma (Fig. 2). Stains with congo red and thioflavin T did not demonstrate any amyloid deposition in the stroma. In some foci, this resembled a carcinoid, with islands of tumor cells separated by a uniform fibrovascular stroma. There were no glandular or papillary structures in the tumor. Vascular invasion was not demonstrable. No inflammation was noted.

The tumor cells were round, polyhedral, or spindle-shaped, with eosinophilic granular cytoplasm. Their nuclei were uniform, oval, and had a fine granular chromatin pattern and occasional small nucleoli. Only occasional mitoses were present.

Electron microscopy. The cells were arranged in continuous solid sheets, with no evidence of follicular, acinar, or glandular differentiation. Neither microfollicles nor intracytoplasmic lumina were noted. The nuclei showed no polarizing tendency and there were no recognizable basal lamina. A few scattered loose attachment zones were present where the cells were closely aligned.

The cells contained variable amounts of membrane-bound, electron-dense, secretory granules ranging from 100 to 400 nm in diameter; most averaged 200 to 250 nm (Fig. 3). These granules

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TABLE 1. SUMMARY OF LITERATURE DATA ON I-131 UPTAKE BY MEDULLARY THYROID CARCINOMA, OR USE IN THERAPY OF THE TUMOR

Question	Literature Data
Does medullary carcinoma, in the thyroid, accumulate radioiodide?	A. When masses are 1 cm or less in size, 75% can not be detected (are not "cold") by imaging (*1*). This is most likely due to a resolution problem, but function in the regions is a possibility.
	B. Before surgery, images (I-131 or Tc-99m) of 29 patients with medullary thyroid carcinoma showed 6/29 (21%) had uptake in the lesions (size 1.5–8 cm diam) (*2*).
Can radioiodide be used to treat medullary carcinoma of the thyroid?	A. In familial type of medullary thyroid carcinoma, no iodide uptake in the tumor was demonstrable by autoradiography, 24 hr after administering I-125 or I-131 (*3*).
	B. Of 10 patients with medullary thyroid carcinoma given I-131, ". . . in none did the tumor or its secondaries show uptake." (*4*)
NEGATIVE	C. Of 72 tabulated cases, six had I-131 as part of the therapy. However, there was no documentation that the tumor accumulated radioidide (*5*).
	D. One patient was given I-131 as well as lobectomy and external radiation (*6*). No evidence was noted that the tumor accumulated radioiodide.
	A. Although the patient appeared to respond to I-131 therapy, (fall in calcitonin), no evidence was presented that the tumor accumulated I-131 (*7*). The effect might have been related to a high concentration of I-131 in nearby thyroid tissue with radiation of tumor tissue in continuity.
POSITIVE	B. The patient had two therapeutic doses of radioiodide (*8*). There appeared to be a response (fall in calcitonin), but tumor uptake of the I-131 was not shown. Again, radiation by continuity may have occurred.
	C. I-131 uptake was shown in the tumor by imaging (but not in a biopsy specimen 16 hr after the dose was given). Much of the radioiodide "flushed" after a dose of perchlorate, suggesting that it was not organified (*9*).
	D. The tumor and its metastases took up I-131. This largely flushed after perchlorate (*10*).

showed an electron-dense, homogeneous matrix closely applied to a limiting membrane without a detectable spacing or halo. The granules were morphologically identical to so-called type II secretory granules found in C-cells and medullary carcinoma cells of the thyroid gland; some investigators have demonstrated such granules to contain calcitonin by electron immunochemistry (*11,12*). The granules were present in all the cells. Occasional cells showed large numbers of the granules. The nuclei were variable in shape but fairly regular in size. The nuclear contours were predominantly smooth, although irregular, and deeply invaginated nuclei were also seen. Nucleoli were prominent. The interstitial areas supporting the tumor cells contained collagen but no masses of amyloid fibrils.

Immunohistochemistry. Immunoperoxidase on both the original and the metastatic tumor showed strong cytoplasmic positivity for thyroglobulin (Fig. 4). Immunoperoxidase for calcitonin was negative. Twenty-four hours after administration of an oral dose of 2 mCi of I-131 as sodium iodide, a whole-body rectilinear scan was performed (Fig. 5, left). Because of demonstrated uptake of radiotracer in the neck and chest lesions, the patient was given an oral dose of 107 mCi of sodium [I-131]iodide. She did not do well, and radiographically the pulmonary lesions showed progression (Fig. 1, bottom).

There was progression of shortness of breath and occasional hemoptysis. A repeat whole-body radioiodide scan was performed 77 days after the first (Fig. 6, center); neck and pulmonary lesions were still present. In addition, the liver uptake on the initial whole-body image was now more prominent. The radioiodide uptake in the liver corresponded to a defect demonstrated on a radiocolloid image of the organ. The patient's disease progressed, and she was treated again (271 mCi of I-131). At 104 days after the second study (181 days after the initial one) a third whole-body image was made ($Na^{131}I$ by mouth. Massive uptake was still present in the neck and thorax, with activity either in the bowel or abdominal organs (Fig. 5, right). Before each of the whole-body images, the patient had been off thyroid medication for 2 wk. Her disease progressed rapidly following the second radioiodide therapy. Following her initial therapeutic dose, she was monitored in two ways. The first was by use of a survey meter, placed at 1 meter. Frequent counts, obtained over the first four days, were plotted semilog. to show whole-body retention as a function of time (Fig. 6). The turnover half-time was approximately one day. The second monitoring technique was by means of a three-inch NaI crystal-uptake probe. Both right and left hemithorax areas were counted while the neck was shielded by means of lead. The thoracic turnover half-time was also approximately one day. On day 5 (after administration of radioiodide) the neck mass was biopsied. A blood sample was obtained at the same time. Each specimen was weighed and counted for radioactivity. The ratio [activity/mg tumor]/[activity/mg blood] was 5.1.

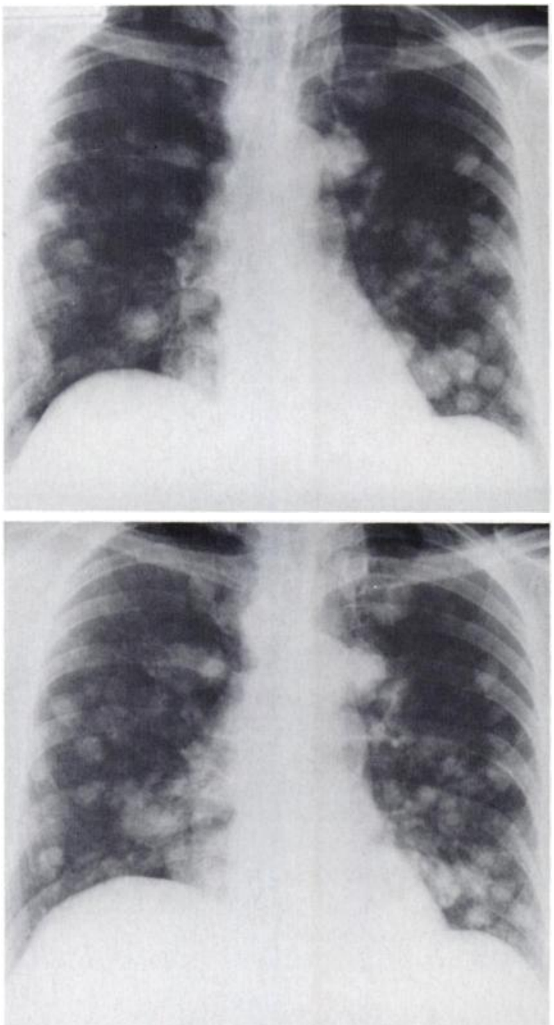

FIG. 1. Upper radiograph was taken on December 14, 1980. Follow-up study (lower) was done on March 18, 1981.

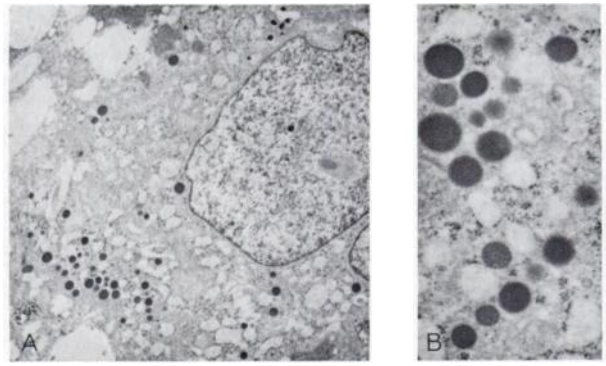

FIG. 3. A. Electron microscopy of tumor cells containing secretory granules (X 9,980). B. Same, at higher magnification of electron-dense secretory granules (X 31,340). Morphologically they are consistent with secretory granules of medullay carcinoma.

DISCUSSION

While sodium[^{131}I]iodide has been used in the treatment of medullary thyroid carcinoma (Table 1), there are few cases in which lesions were found to concentrate the radiotracer. We must consider a number of possible explanations.

1. In the present case, the tumor resembled a medullary thyroid carcinoma by both light and electron microscopy. However, the tissue did not reveal the presence of calcitonin by means of immunoperoxidase. Thyroglobulin was demonstrated. A follicular-cell origin was thus a distinct possibility.

2. Kameda and coworkers (*13*) believe that, at least in dogs, follicles in the C-cell complexes can incorporate radioiodine; further, they state that thyroid follicles can arise from the ultimobranchial bodies. Whether such interconversions can occur in humans is unknown. Kakudo and coworkers (*14*) described unusual cytoplasmic inclusions in medullary carcinoma of the thyroid. Whether these can be used to classify the cells of origin is unknown.

3. The possibility that some patients have two distinct tumors, or two tumor components, is worthy of consideration. Thus, medullary and follicular-cell types might both be involved in rare cases. Immune staining may have an important role to play, in efforts to separate out the nature of the underlying cell type(s). There are, of course, many reports in the literature of patients having two or more simultaneous tumors of different histological types, including "synchronous carcinomas" (*15*). There was uptake of radioiodide by the neck tumor and its metastases (and slight retention, to give a tumor/blood ratio of ~5 at 5 days after I-131 therapy). However, the overall rate of decline of retained radioiodide was rapid ($t_{1/2}$ = 1 day). This suggests that a more satisfactory therapeutic effect might be achieved if tumor iodide turnover could be slowed. Lithium salts inhibit iodide release from the thyroid (*16*) and have not been proposed for the treatment of hyperthyroidism. The use of such lithium compounds might be

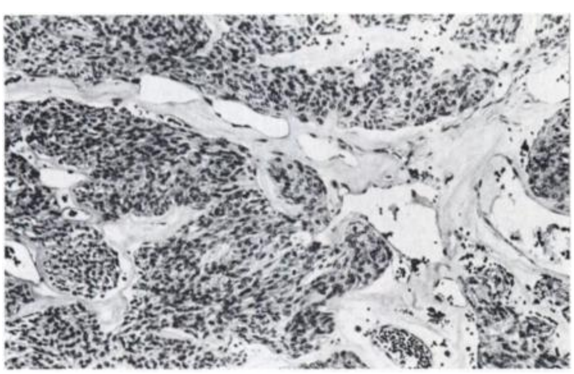

FIG. 2. Photomicrograph of section of tumor (H and E stain, ×172). Undifferentiated carcinoma is arranged in nests with broad cellular trabeculae but no follicular to papillary differentiation.

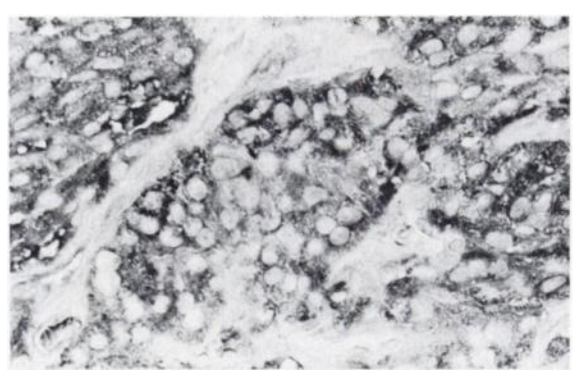

FIG. 4. Immunoperoxidase test for thyroglobulin (X 384). Carcinoma shows cytolasmic positivity.

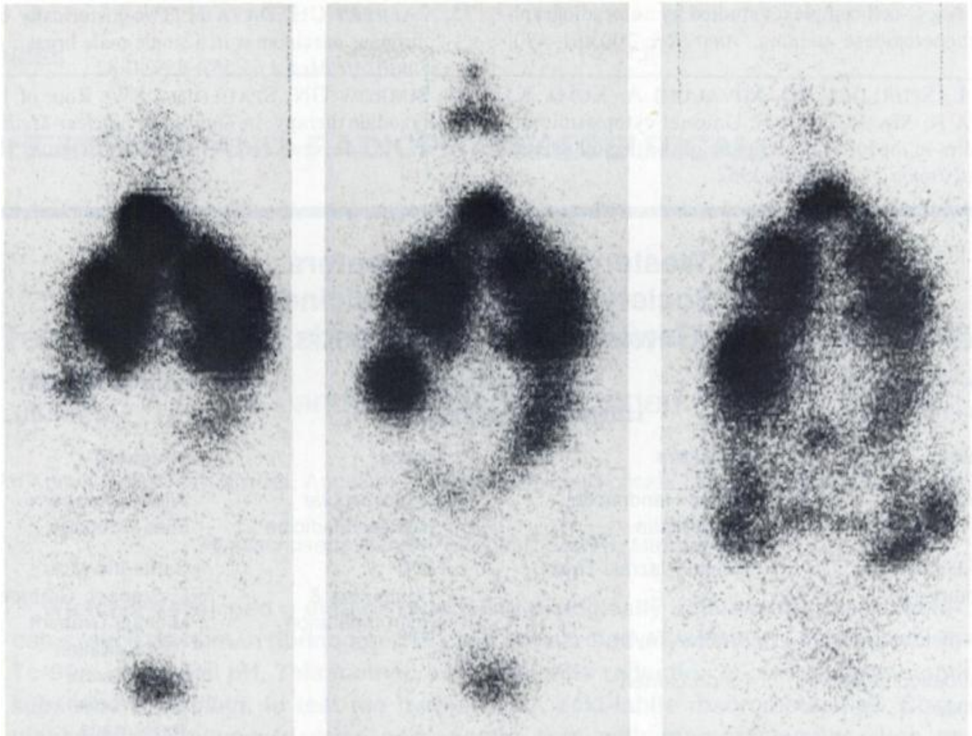

FIG. 5. Anterior rectilinear scans obtained (left to right) on Dec. 11, 1980, Feb. 26, 1981, and June 10, 1981. Doses ($Na^{131}I$ by mouth) and timing were: 2 mCi + 24 hr; 2 mCi + 24 hr; 1 mCi + 48 hr. Between first and second images a therapeutic dose of 107 mCi had been administered; between second and third 250 mCi.

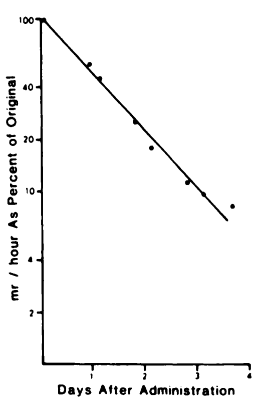

FIG. 6. Semilogarithmic plot of radiation at one meter from patient, as a function of time after administration of radioiodide.

warranted in an attempt to prolong iodide retention in the tumor and in its metastases.

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