

Medullary Thyroid Carcinoma: Radiotracers in Therapy and Evaluation of Primary or Metastatic Sites

Medullary carcinoma of the thyroid (MCT) presents an opportunity to follow the biology of a tumor with several interesting properties.

1. Although some cases of MCT occur spontaneously (or at least in isolated fashion), others represent a familial incidence of the disorder (1). Thus, relatives need screening for the presence of MCT once the diagnosis is established in one individual.

2. MCT secretes calcitonin into the blood stream. This tumor marker and other biochemical indicators (2) herald the presence of MCT. Screening for MCT in families involves the study of blood, by thyroid venous catheterization or peripheral sampling, for the presence of elevated calcitonin levels. This can be carried out on baseline aliquots and again after provocative testing to stimulate calcitonin release by means of pentagastrin or calcium infusion (3).

From a broader viewpoint, MCT is but one of a number of tumors of the endocrine system that produce quantities of biochemical markers entering the blood stream. Other examples are the liberation of epinephrine-like compounds by pheochromocytomas, and the passage of thyroglobulin from differentiated thyroid malignancies into the general circulation. MCT was differentiated from other thyroid tumors only about 25 yr ago (4). In addition to the usual histologic appearance, there has been recognition that instances of thyroid carcinoma can exist with a mixed medullary and follicular pattern (5) or as a follicular carcinoma with an architectural pattern that simulates MCT (6). For workers in nuclear medicine, MCT poses a challenge, since the use of radionuclides affects at least seven areas involving the diagnosis, treatment, and follow-up of patients with this tumor.

1. Radioimmunoassay is utilized to quantify the circulating levels of calcitonin. Simpson and associates have placed this assay into the perspective of managing patients with MCT (7).

a. Individuals with MCT who, following pentagastrin stimulation, have undetectable or normal calcitonin levels after treatment of their tumor; are probably cured.

b. In some patients, after apparently successful therapy of MCT, circulating immunoreactive calcitonin levels may remain elevated for some months before returning to normal values. DeVita has commented on the phenomenon of slow resorption of destroyed tumor cells (8). Perhaps this delayed resorption accounts for the prolonged liberation of calcitonin into the blood stream.

c. When calcitonin levels remain elevated after therapy, even without apparent tumor, additional therapy is indicated, since there are probably microscopic foci of MCT present (7).

There has been little exposition of the relationship between the MCT mass and the circulating blood level of calcitonin (C). An initial assumption is that the amount of calcitonin liberated is directly proportional to the mass (M) of calcitonin in the tumor and its rate constant for release. Further, the removal of calcitonin from the blood stream (and likely from other extracellular fluids) is probably dependent upon circulating levels. Thus we can write:

$$\frac{dC}{dt} = a.M - k.C$$

There are few data in the literature to permit testing of this hypothesis. The content of calcitonin in each tumor mass, and the rates of release, might be different. Data have to be gathered as to the tumor content of calcitonin and the rate of its release into the blood stream (and rate of removal from the circulation), to test this initial approach for following the course of therapy of MCT.

2. Thyroid imaging has an interesting role to play in evaluating patients with MCT. It has been pointed out that, in almost all cases of familial MCT, the tumor occurs bilaterally (3). Thyroid imaging may show lesions in both lobes in such cases. We have summarized some of the literature



FIG. 1. Posterior thoracic image (Tc-99m MDP) from 38-yr-old woman with MCT. Extensive lesions in ribs and vertebrae can be noted. Decreased activity in some lower vertebrae is probably related to external radiation.

on the appearance of thyroid lesions in MCT, and the occasional ability of these tumors to transport iodide and its analogs (6).

3. A number of radiotracers can occasionally localize in MCT. Some of those that may delineate the tumor are the following.

a. MCT, both within the neck (9) and at distant sites, can accumulate the Tc-99m phosphates used for bone imaging. Johnson and associates (10) report in this edition of the *Journal* that eight out of 30 patients (27%) with MCT showed lesions in bone images. Two individuals showed only extraosseous uptake, while two others had both extraosseous accumulation and bone lesions. Hence, the extraosseous uptake was seen in half of those who had abnormal deposition of the Tc-99m phosphates. The known calcification of many MCT lesions may at least partly account for this radiotracer localization.

b. While most areas of MCT do not concentrate pertechnetate or radioiodide, some patients have lesions that do take up these tracers (6).

c. There appears to be little experience concerning the roles of radiothallium and radiogallium in delineating MCT. Senga and associates (11) reported a case with uptake of Tl-201 thallos chloride in a thyroid lobe containing MCT. The area did not accumulate Ga-67 citrate. A case reported by Parthasarathy and co-workers showed uptake of radiothallium, pertechnetate, and radioiodide by MCT (16).

4. Radiotracers may have a role to play in detecting the spread of MCT to areas outside of the neck. The high incidence of disease found in bone and in liver by Johnson and associates (10) raises the question of whether all patients with MCT should be screened by bone and liver scintigrams, or whether other modalities would give a higher "yield" in determining the extent of this tumor. Our experience with MCT has shown a predilection of tumor spread to vertebral bodies and ribs (Fig. 1).

5. Since calcitonin is a marker for MCT, does a radiolabeled anticalcitonin have a role to play in locating the tumor? A report by Gautvik and co-workers has shown promise, using a rat MCT and a rabbit antiserum against intact synthetic hormone (12). With I-131 as the immunoglobulin radiolabel, and In-113m as a blood-pool marker, tumor tissue had a ratio of I-131/In-113m from 3-6 times that of other areas. This study points out potential problems in the anti-calcitonin approach. First, there is usually a significant quantity of calcitonin in the blood stream. Labeled antibody binding to the intravascular calcitonin produces a high blood background, which has to be taken into account. This is the reason for a second intravascular label such as In-113m (which binds to transferrin). Second, it is not clear why an anticalcitonin molecule would label intact cells. Perhaps there are calcitonin or preprocalcitonin (2) moieties on the cell surface. The use of monoclonal antibodies against calcitonin or preprocalcitonin deserves investigation—as does the use of

antibody fragments—in an effort to speed disappearance of the label from the blood pool. Pharmacologic interventions might have a role to play during imaging. For example, magnesium infusion lowers serum calcitonin levels (13); this might reduce background interference. In addition, MCT also puts CEA into the blood stream (14, 15); a dual-label approach might be feasible, with antibodies to CEA as well as to calcitonin.

6. Can radiopharmaceuticals be used in the therapy of MCT? Two approaches may hold promise. The first is utilization of labeled anticalcitonin or labeled antibodies to other components of MCT cells. If the studies discussed above are successful in producing labeled antibody of high specific activity, then not only are diagnostic uses opened up, but therapy also becomes possible. Second, some MCT lesions do accumulate radioiodide. We have noted that rapid turnover of the radiotracer may prevent successful use of I-131 in the therapy of these cases; agents that delay radionuclide turnover were proposed as therapeutic adjuncts (6).

7. What role does nuclear medicine play in following the effects of treatment on MCT? The major tool is use of blood assays for calcitonin. As discussed in Category 1 above, the circulating level of calcitonin is a major determinant in following MCT. Whether other procedures (such as liver and bone imaging) have a role in showing regression of lesions must still be determined. A radiolabeled anticalcitonin might be a major tool in following the extent and the regression of MCT lesions after treatment. In addition, since MCT produces a variety of other markers, such as neuron-specific enolase (17), there may be other possibilities for attaching antibodies to the tumor.

The report of Johnson and associates (10) thus opens a wide area for study. Nuclear medicine may have many roles in the evaluation and therapy of MCT. The recent report of the accumulation of Tc-99m DMSA by medullary thyroid carcinoma holds promise of a potentially useful diagnostic adjunct. (18).

RICHARD P. SPENCER
University of Connecticut
Health Center
Farmington; Connecticut

ACKNOWLEDGMENT

Supported by USPHS CA 17802 from the National Cancer Institute.

REFERENCES

1. NORTON JA, FROOME LC, FARREL RE, et al: Multiple endocrine neoplasia type IIb: the most aggressive form of medullary thyroid carcinoma. *Surg Clin North Am* 59:109-118, 1979
2. ROOS BA, HUBER B, BIRNBAUM RS, et al: Medullary thyroid carcinomas secrete a noncalcitonin peptide corresponding to the carboxyl-terminal region of preprocalcitonin. *J Clin Endo Metab* 56:802-807, 1983
3. WELLS SA JR, BAYLIN SB, JOHNSRUDE IS, et al: Thyroid venous catheterization in the early diagnosis of familial medullary thyroid carcinoma. *Ann Surg* 196:505-511, 1982
4. HAZARD JB, HAWK WA, CRILE GJ: Medullary (solid) carcinoma of the thyroid: a clinicopathological entity. *J Clin Endocrinol Metab* 19:152-161, 1959
5. HALES M, ROSENAU W, OKERLUND MD, et al: Carcinoma of the thyroid with a mixed medullar and follicular pattern. *Cancer* 50:1352-1359, 1982
6. SPENCER RP, GARG V, RAISZ LG, et al: Radioiodide uptake and turnover in a pseudo-medullary thyroid carcinoma. *J Nucl Med* 23:1006-1010, 1982
7. SIMPSON WJ, PALMER JA, ROSEN IB, et al: Management of medullary carcinoma of the thyroid. *Am J Surg* 144:420-422, 1982
8. DEVITA VT JR: The relationship between tumor mass and resistance to chemotherapy: implications for surgical adjuvant treatment of cancer. *Cancer* 51:1209-1220, 1983
9. HARTSHORNE MF, KARL RD, JR, CAWTHON MA, et al: Multiple imaging techniques demonstrate a medullary carcinoma of the thyroid. *Clin Nucl Med* 8:628-629, 1983
10. JOHNSON DG, COLEMAN RE, MCCOOK TA, et al: Bone and liver scans in medullary carcinoma of the thyroid. *J Nucl Med* 25:419-422, 1984
11. SENGA O, MIYAKAWA M, SHIROTA H, et al: Comparison of Tl-201 chloride and Ga-67 citrate scintigraphy in the diagnosis of thyroid tumor: concise communication. *J Nucl Med* 23:225-228, 1982
12. GAUTVIK KM, SVINDAHL K, SKRETTEING A, et al: Uptake and localization of ¹³¹I-labeled anti-calcitonin immunoglobulins in rat medullary thyroid carcinoma tissue. *Cancer* 50:1107-1114, 1982
13. ANAST C, DAVID L, WINNACKER J, et al: Serum calcitonin-lowering effect of magnesium in patients with medullary carcinoma of the thyroid. *J Clin Invest* 56:1615-1621, 1975

14. ISHIKAWA N, HAMADA S: Association of medullary carcinoma of the thyroid with carcinoembryonic antigen. *Br J Cancer* 34:111-115, 1976
15. HAMADA S, ISHIKAWA N, YOHSI M, et al: Roles of circulating carcinoembryonic antigen and calcitonin in diagnosis of medullary thyroid carcinoma: a comparative study. *Endocrinol Jpn* 23:505-510, 1976
16. PARTHASARATHY KL, SHIMAOKO K, BASHI SP, et al: Radiotracer uptake in medullary carcinoma of the thyroid. *Clin Nucl Med* 5:45-48, 1980
17. TAPIA FJ, POLAK JM, BARBOSA AJ, et al: Neuron-specific enolase is produced by neuroendocrine tumors. *Lancet* 1:808-811, 1981
18. OHTA H, YAMAMOTO K, ENDO K, et al: A new imaging agent for medullary carcinoma of the thyroid. *J Nucl Med* 25:323-325, 1984