

A New Imaging Agent for Medullary Carcinoma of the Thyroid

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Thyroid scintigraphy, using $^{99m}\text{Tc(V)}$ dimercaptosuccinic acid, was performed in four patients with pathologically confirmed medullary thyroid carcinoma and elevated serum calcitonin values. Significant uptake of the tracer was found in the clinically palpable cervical tumor masses, metastatic sites, and residual tumor. This finding, probably specific for medullary thyroid carcinoma, could be of great use in the diagnosis and the surgical follow-up.

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Iodine-123 as iodide, and Tc-99m as pertechnetate, are the most widely used agents for screening thyroid diseases, but they yield photopenic images of medullary thyroid carcinoma (MTC) originating from C cells (1,2). The secretion of large amounts of calcitonin (3) and CEA (4) have provided reliable tumor markers for MTC. In the search for a diagnostic method to provide a positive image, Tl-201 chloride (5), Tc-99m-tagged phosphates (6,7) and in some cases radioiodine (8,9) have been tried, but their reliability has been questioned.

Recently, a new conceptual approach built on the design of $^{99m}\text{Tc(V)}$ dimercaptosuccinic acid [Tc(V)-DMS], a complex containing a TCO_4^{-3} core, has been shown to exhibit characteristics comparable to those of PO_4^{-3} (10–12). In our concern for further diagnostic exploration of MTC, we made scintigraphic studies in four patients using the newly developed Tc(V)-DMS, and compared its usefulness and other relevant clinical data with those from patients with other thyroid malignancies.

MATERIALS AND METHODS

Studies were performed on four patients with MTC (two untreated and two postoperative), ten untreated patients with papillary or follicular adenocarcinoma, one patient with undifferentiated carcinoma, and one with malignant lymphoma.

For the present study, commercial Tl-201 chloride, Ga-67 citrate, and pertechnetate (Tc-99m) were used. The lyophilized kit of Tc(V)-DMS contains 1.36 mg of dimercaptosuccinic acid, 1.26 mg of NaHCO_3 , 0.11 mg of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, and 30 mg of glucose. This kit is now being made available.* Labeling was performed by the addition into the kit of 0.1 ml of 7% NaHCO_3 with 2–3 ml of pertechnetate with the desired activity. Purity of the complex

was analyzed by thin-layer chromatography (TLC) ([Merck silica gel, developed with *n*-butanol/acetic acid/ H_2O (3:2:3)], and no free pertechnetate or other Tc-99m derivative was detected.

Anterior scintigrams were made 120 min after i.v. administration of 10 mCi Tc(V)-DMS, using a conventional gamma camera.

CASE REPORTS

Case 1. A 42-yr-old woman was referred to our hospital with a 10-yr history of an enlarging right neck mass, making opening of the mouth difficult. A month before referral she noticed difficulty in breathing, palpitation, and mild pain in neck mass.

She was clinically euthyroid and results of thyroid function tests were normal. Routine laboratory studies included urinalysis, complete blood counts, and blood chemistry. In addition, there was elevated serum calcitonin in the order of 24 ng/ml (normal range <0.1 ng/ml) and a CEA level of 132 ng/ml (normal range <10 ng/ml).

Neck TCT scans demonstrated a large right neck mass originating from right thyroid lobe, with deviation of the trachea toward the left. The neck mass was found to be MTC by histopathological diagnosis.

Case 2. A 57-yr-old woman, with a 1-mo history of left anterior neck tumor, sustained an aspiration biopsy of the thyroid, and MTC was suspected. She was referred to our hospital for a Tc(V)-DMS scintigram. She was clinically euthyroid and general laboratory findings were normal, but serum calcitonin was higher than 6.4 ng/ml and the CEA level was 36 ng/ml.

Case 3. A 50-yr-old man, with an enlarged cervical mass of 10 mo duration, was operated on for MTC. One year later the serum calcitonin level was found raised, and palpation identified one nodule in the anterior neck. Serum calcitonin was then 3.2 ng/ml.

Case 4. A 54-yr-old man, admitted with complaints of muscle weakness, underwent partial thyroidectomy 15 yr ago, but little

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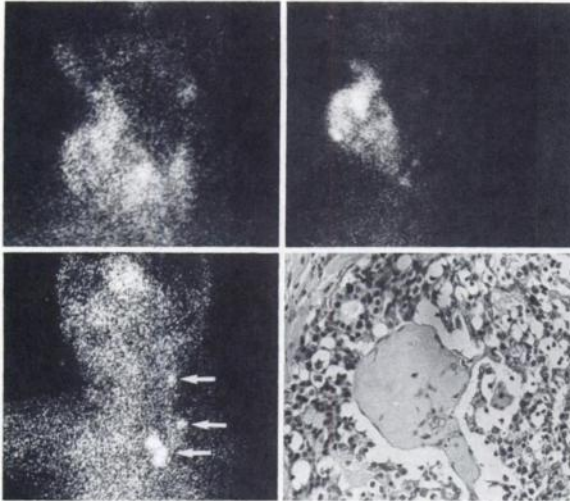


FIG. 1. Preoperative scintigrams of patient (Case 1) with medullary thyroid carcinoma: Tl-201 chloride (upper left), and Tc(V)-DMS (upper right). Patient's postoperative Tc(V)-DMS scintigram is at lower left. Note lack of Tc(V)-DMS accumulation in normal part of left thyroid lobe, whereas Tl-201 accumulates in both carcinoma and normal tissues. At lower right is section of lymph node carrying metastasis from medullary carcinoma of thyroid ($\times 100$). Dense acellular areas were shown to be amyloid. Postoperatively, serum calcitonin level remained high (2.2 ng/ml).

other information data was available. Our laboratory findings showed serum calcitonin at 2.2 ng/ml and ACTH at 275 pg/ml (normal range 22–175 pg/ml). He was diagnosed as ectopic ACTH-producing tumor with MTC. At the time of imaging, serum calcitonin values as high as 315 ng/ml were found. Autopsy revealed MTC invasion of the mediastinum.

RESULTS

In Case 1, the TCT image suggested the presence of tumor, however, no sequestration of (Tc-99m) pertechnetate was observed in the neck tumor. Both Tl-201 chloride and Tc(V)-DMS accumulated in the lesions (Fig. 1). There was no significant uptake of Tc(V)-DMS in the normal left thyroid lobe, salivary glands, stomach, or bones, but Tl-201 accumulated in normal thyroid tissues. After the excision of right neck mass, serum calcitonin and CEA levels subsided, although still remaining high at 2.2 ng/ml and 33 ng/ml, respectively. Scintigrams made postoperatively with Tc(V)-DMS clearly revealed nonpalpable residual tumors in the left thyroid lobe (Fig. 1).



FIG. 2. Preoperative Tc(V)-DMS scintigram of patient (Case 2) with medullary thyroid carcinoma. Accumulation of Tc(V)-DMS in lesions extending into thoracic cavity (left) was recognized and confirmed by operation. Serum calcitonin level was higher than 6.4 ng/ml. Center: Tc(V)-DMS accumulation in neck mass (arrow) in patient (Case 3) with MTC after partial thyroidectomy. Serum calcitonin concentration was 3.2 ng/ml. Right: Scintigram taken postoperatively with Tc(V)-DMS in patient with MTC (Case 4). At time of image, serum calcitonin level was 315 ng/ml. Tc(V)-DMS scintigram demonstrates mediastinal metastatic sites (arrow).

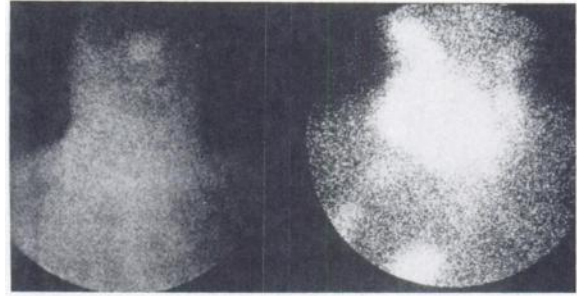


FIG. 3. Scintigrams of patient with follicular adenocarcinoma of thyroid using Tc(V)-DMS (left), and Tl-201 chloride (right). There was no accumulation of Tc(V)-DMS, but Tl-201 accumulated in neck tumor.

In Case 2, accumulation of Tc(V)-DMS in the lesions extending to the thoracic cavity was recognizable, but there was no significant uptake of Tc(V)-DMS in the normal thyroid tissue (Fig. 2). Surgery and histopathological diagnosis revealed MTC extending into the thoracic cavity.

Cases 1 and 2 led us to do scintigraphic studies on two other postoperative MTC patients and with elevated serum calcitonin values. The Tc(V)-DMS accumulated in metastatic sites in the neck and mediastinum, as shown in Fig. 2. However, in ten patients with papillary or follicular adenocarcinoma, one patient with undifferentiated carcinoma, and one patient with thyroid lymphoma, no significant uptake of Tc(V)-DMS was observed (Figs. 3 and 4). In these two cases the tumors were well defined by Tl-201 chloride and Ga-67 citrate, respectively.

DISCUSSION

In most MTC cases, photopenic radioiodine and pertechnetate thyroid images have been obtained, and such thyroid scintigrams have been considered ineffective for detecting MTC (12,13). Some reports on the use of Tl-201 chloride and Tc-99m phosphates have claimed positive images for MTC, but Tl-201 accumulates in almost all solid thyroid tumors and also in normal thyroid tissue.

The new conceptual approach based on Tc(V)-DMS provided plausible rationale for screening four patient with MTC. In every case studied we found intense accumulation of Tc(V)-DMS in MTC and its metastatic sites. Although at present a complete study of only one case (Case 1) was achieved, additional information gathered from the other three cases yielded adequate evidence for the usefulness of Tc(V)-DMS in the diagnosis of MTC. In postoperative patients (Cases 3 and 4), detection of the metastasis or residual tumor was of great clinical value. Moreover,

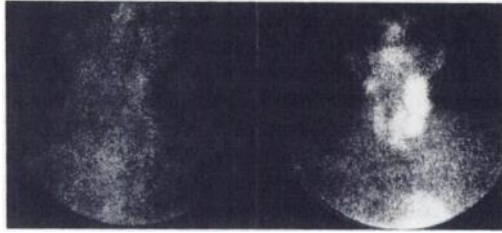


FIG. 4. Scintigrams of patient with malignant lymphoma of thyroid, using Tc(V)-DMS (left), and Ga-67 citrate (right). There was no apparent accumulation of Tc(V)-DMS, but marked uptake of Ga-67.

the accumulation of Tc(V)-DMS was considered specific, since no significant uptake of Tc(V)-DMS was observed in other thyroid malignancies. Neither was there any significant uptake in normal thyroid, salivary glands, or adult bone.

On the other hand, the finding of elevated serum calcitonin provides a reliable tumor marker for the diagnosis of MTC, and its correlation with the turnover of calcium or phosphate ions is relevant. In the cases analyzed, the level of calcitonin ranged from as low as 3.2 to as high as 315 ng/ml, but in every case the scintigrams showed adequate accumulation of Tc(V)-DMS. Although we find no such interrelation in the literature, this Tc(V)-DMS, designed as an orthophosphate-related new Tc-99m radiopharmaceutical, seems to offer great potentiality in the evaluation of size and sites of MTC and its metastases.

Further studies are necessary to define the processes that concentrate Tc(V)-DMS and its role in thyroid nodules, but its usefulness as a radiotracer for the diagnosis and follow-up of MTC is evident. Its value as a tumor-seeking agent for other malignant diseases is under study.

FOOTNOTE

* Daiichi Radioisotopes, Tokyo, Japan.

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