Localization of Recurrent Medullary Thyroid Carcinoma with Technetium-99m-Methoxyisobutylnitrile Scintigraphy: A Case Report

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This case report demonstrates the successful localization of metastatic medullary thyroid carcinoma with ^{99m}Tc-labeled methoxyisobutylnitrile (MIBI). Disease recurrence was initially localized using ^{201}Tl and by immunoscintigraphy with ^{111}In-labeled anti-carcinoembryonic antigen (anti-CEA) antibody fragments. Scintigraphy with ^{99m}Tc-MIBI yielded higher target-to-background ratios than ^{201}Tl or ^{111}In-anti-CEA. Technetium-99m-MIBI may be a useful agent in the localization of recurrent medullary thyroid carcinoma.

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Medullary thyroid carcinoma (MTC) is a relatively uncommon tumor derived from the parafollicular C-cells of the thyroid. These cells, which are neuroectodermal in origin are not involved in thyroid hormone synthesis, but secrete the hypocalcaemic hormone calcitonin. MTC accounts for 2%–12% of thyroid malignancies with an annual incidence of 35–60 new cases per million population (*1*). It may occur in sporadic or less commonly familial forms, when it may form part of a multiple endocrine neoplasia (MEN) syndrome. Radioimmunoassays for serum calcitonin and carcinoembryonic antigen (CEA) are used for early detection of disease recurrence, but localization of metastatic tissue can be difficult. Thallium-201 has been used to localize MTC metastases (*2*) and as the myocardial perfusion agent methoxyisobutylnitrile (MIBI) (Cardiolite, Du Pont, N. Billerica, MA) has some biologic properties similar to ^{201}Tl, we therefore postulated that ^{99m}Tc-MIBI might also localize MTC metastases. This case report details our initial patient study.

CASE REPORT

A 46-yr-old female with MTC diagnosed in 1988, underwent total thyroidectomy and modified block dissection of right cervical nodes. Twenty-one of 58 (36%) nodal specimens were histologically positive for tumor. Postoperatively, a small thyroid remnant was identified by [^{99m}Tc]pertechnate scanning and treated with an ablative dose of ^{131}I. Serum CEA and calcitonin levels, which were elevated preoperatively, returned to the normal range after surgery. Postoperative surveillance was performed by clinical examination and serum CEA at 6-mo intervals. Serum CEA levels began to rise in early 1990 and serum calcitonin levels were also elevated. Repeated physical examination did not detect a site of recurrence.

A whole-body scintiscan was performed at 2 and 24 hr following intravenous injection of 74 MBq ^{123}I-metaiodobenzylguanidine (MIBG), but failed to detect metastases. Total-body scintigraphy started 30 min postinjection of 74 MBq ^{201}Tl-chloride revealed intense focal uptake anterolaterally in the left side of the root of the neck (Fig. 1A). Immunoscintigraphy was performed 96 hr postinjection of 1 mg anti-CEA F(ab')$_2$ fragment labeled with 120 MBq ^{111}In. Abnormal antibody uptake was once more seen in the lower left neck anterolaterally (Fig. 1B).

Informed consent was obtained prior to intravenous injection of 370 MBq ^{99m}Tc-MIBI. Anterior, posterior, and lateral planar images were obtained, starting at 30 min and SPECT images, starting 4 hr postinjection. A discrete "hot" lesion was seen in an area identical to that identified with ^{201}Tl and ^{111}In-anti-CEA scanning (Fig. 1C). SPECT also was performed 4 hr postinjection of ^{99m}Tc-MIBI. Two discreet "hot" lesions were seen, one lying superficially and a second immediately deep to the first (Fig. 1D). All imaging was performed on a GE 400 AC Starport gamma camera interfaced to an MDS A^2 nuclear medicine computer. Indium-111-anti-CEA scanning was performed with a medium-energy collimator, otherwise a low-energy general-purpose collimator was used. Target-to-background (T:B) ratios were calculated using the average count rate per pixel in a region of interest including the tumor divided by the average count rate per pixel for a region in adjacent structures. The interval between scans was 3 wk in all cases. Technetium-99m-MIBI scanning was performed three days preoperation. Subsequently, non-contrast computed x-ray tomography of the neck was performed at 8-mm intervals from first cervical vertebra to first thoracic vertebra inclusive. Metastases were not detected.

At operation, a 2-cm diameter node was identified behind the sterno mastoid muscle. Frozen section examination confirmed that >90% of the node had been replaced by tumor. A modified neck dissection identified another node 1.4 cm in diameter lying

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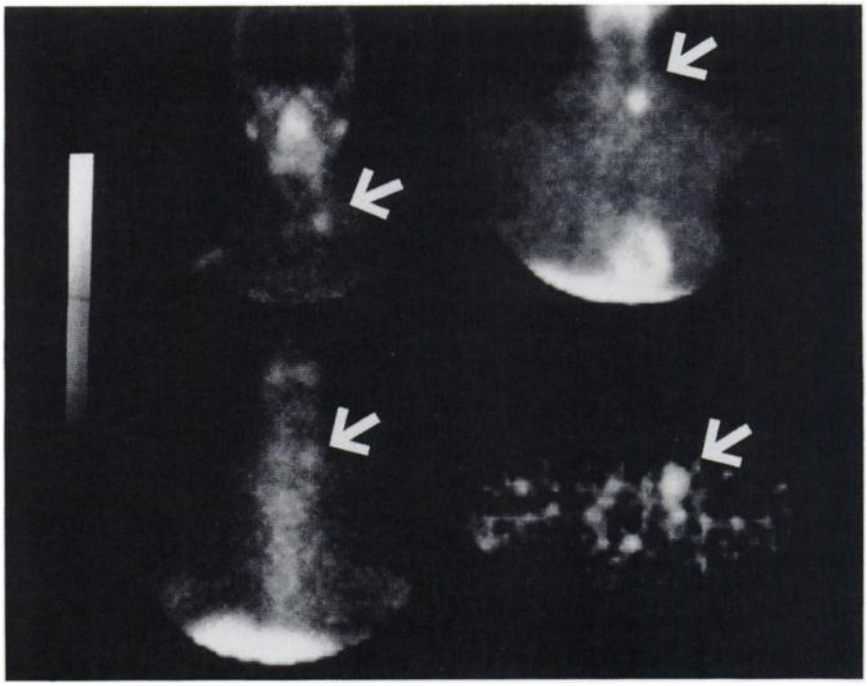

FIGURE 1. Anterior planar images obtained with ^{201}Tl (A), ^{111}In-anti-CEA (B), ^{99m}Tc-MIBI (C), and SPECT transaxial image with ^{99m}Tc-MIBI (D).

deep to the internal jugular vein, which on histologic examination was completely replaced by tumor. Repeat planar scanning of the neck with ^{99m}Tc-MIBI and ^{201}Tl on postoperative Days 7 and 10, respectively, did not demonstrate residual abnormal accumulation.

DISCUSSION

Diagnosis and follow-up of MTC are facilitated by sensitive radioimmunoassays for CEA and calcitonin. Despite an aggressive histologic appearance the tumor may progress slowly and local recurrences, when identified, can be effectively dealt with surgically. Localization of tumor recurrence, however, is often difficult.

A variety of agents have been reported to be useful for MTC imaging, including MIBG, ^{201}Tl, ^{99m}Tc (pentavalent) dimercaptosuccinic acid and radiolabeled monoclonal whole antibodies or fragments (*2*).

While the binding of radiolabeled anti-CEA antibody to CEA surface antigens on tumors is highly specific, the quality of the scinti-images obtained depends on a number of additional factors, including tumor size, vascularity, capillary permeability, density of CEA surface antigens, tumor retention time of antibody/antigen complexes, as well as the many factors affecting background radioactivity.

Antibody fragments were used in this case since they have been reported to give better tumor penetration and faster blood-pool clearance resulting in improved T:B ratios (*2*). Successful imaging of MTC has been reported to be seen most often in patients with elevated serum CEA; tumors > 10 cm^3; and when using SPECT imaging (*2*).

Thallium-201 chloride behaves as a potassium analogue and has been reported to accumulate in highly active cellular tissues which are well vascularized. In myocardial cells the accumulation of ^{201}Tl-chloride has been shown to occur both by active transport, using two Na/K ATPase binding sites, and by passive diffusion along concentration gradients (*3*). Since all metabolically active cells have Na/K ATPase transmembrane transport systems it is likely that these uptake pathways are also present in tumor cells.

Although ^{99m}Tc-MIBI has been observed to accumulate in some neoplastic lesions, including lung (*4,5*), thyroid (*6*) and brain (*7*) tumors, the precise mechanism of tumor localization is still unclear.

Intracellular accumulation of MIBI is promoted by negative transmembrane potentials and it has been proposed that malignant cells, by virtue of their increased metabolic rate, maintain greater negative mitochondrial and transmembrane potentials, thus enhancing intracellular accumulation of ^{99m}Tc-MIBI (*8*).

In this patient, serum CEA and calcitonin levels indicated relapse. Thallium-201 and ^{111}In-anti-CEA scintigraphy both localized tumor in the lower left neck anterolaterally. Planar ^{99m}Tc-MIBI imaging also localized the tu-

TABLE 1
Target-to-Background Ratios

^{111}In-anti-CEA	1.32
^{201}Tl	1.67
^{99m}Tc-MIBI	
Planar at 30 min	2.26
SPECT at 4 hr	1.30

mor at the same site, but with a higher T:B ratio (Table 1). It is unclear why ^{99m}Tc-MIBI should give a higher T:B ratio than ^{201}Tl. Perhaps the partly lipophilic nature of the ^{99m}Tc-MIBI complex permits easier transmembrane passage than the hydrated ionic structure of the thallous cation.

Planar imaging with ^{99m}Tc-MIBI failed to detect the 1.4 cm diameter node, a sensitivity similar to that reported for planar imaging with ^{201}Tl (*9*). The SPECT study provided more precise anatomical detail, as has previously been reported for ^{201}Tl imaging (*9*), and identified a lesion not seen on planar imaging, despite the unexpected decrease in T:B ratio that was observed between the time of planar imaging (30 min) and the time of SPECT imaging (4 hr), (Table 1). This rapid drop in T:B ratio suggests that MIBI retention in tumors may be quite different from the retention seen in myocardial cells.

Technetium-99m-MIBI combines the practical advantages of a kit-based ^{99m}Tc radiopharmaceutical with good T:B ratios and same-day imaging. This case suggests that it may be considered as an alternative radiopharmaceutical in the search for recurrent MTC.

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