Technetium-99m-Tetrofosmin Imaging of Differentiated Mixed Thyroid Cancer

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This report describes the accurate localization of metastatic lesions in a patient with differentiated mixed thyroid cancer using ^{99m}Tc-tetrofosmin imaging. A 66-yr-old women with a cytological diagnosis of follicular thyroid cancer associated with a large amount of goiter changes was studied by ^{99m}Tc-tetrofosmin total-body scintigraphy. No significant tetrofosmin uptake was observed in the thyroid nodules, which mainly showed goiter abnormalities. Abnormal increased tetrofosmin uptake, however, was found in metastatic tumor lesions located in the cervical and dorsal spine as well as in the left lower chest wall and lungs. In conclusion, ^{99m}Tc-tetrofosmin, a new radiopharmaceutical proposed for myocardial perfusion imaging, may be useful in patients with thyroid cancer.

Key Words: technetium-99m-tetrofosmin; total-body imaging; thyroid cancer; metastasis

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Technetium-99m-1,2-bis [bis (2-ethoxyethyl) phosphino] ethane (tetrofosmin) is a new lipophilic technetium-phosphine dioxo-cation proposed for myocardial perfusion imaging (*1,2*). Human biodistribution studies demonstrated thyroid uptake of tetrofosmin (*1*). In particular, thyroid glands show significant early uptake with successive tracer washout so that it is almost undetectable 4 hr after injection (*1*). Previous experimental studies demonstrated that thyroid tetrofosmin uptake is not blocked by perchlorate, therefore thyroid tracer accumulation is not due to free pertechnetate but represents uptake of the ^{99m}Tc complex itself, as described for ^{201}Tl and ^{99m}Tc methoxy isobutyl isonitrile (sestamibi) (*3,4*). In this report, we describe the results of tetrofosmin imaging in a patient with metastatic differentiated mixed thyroid cancer.

CASE REPORT

A 66-yr-old woman with back pain was admitted to our department for diagnostic evaluation. The patient underwent dorsal spine x-ray tomography using antero-posterior and lateral views demonstrating osteolysis of the 12th vertebra. To further evaluate this abnormality, spinal CT and fine-needle aspiration biopsy (FNAB) were also performed. An osteolytic lesion of the 12th dorsal vertebra was detected and FNAB findings documented a metastatic abnormality by well-differentiated follicular thyroid adenocarcinoma.

Successively, the patient underwent diagnostic evaluation of the thyroid gland. Thyroid physical examination showed two solid nodules, one for each lobe. No abnormal lymph nodes were detected in the neck. Laboratory measurements of thyroid function were normal. Serum thyroglobulin was 114 ng/ml (normal value < 50), while carcinoembryonic antigen and tissue peptide antigen levels were in the normal range. The patient underwent US and FNAB of the thyroid, which showed the presence of multiple nodules in an enlarged gland. The two largest nodules were located in the middle of right lobe and in the inferior region of left lobe. FNAB findings of these lesions documented a prevalence of goiter abnormalities associated to the presence of a small amount of atypical cells suggesting well-differentiated follicular thyroid adenocarcinoma. Thyroid scintigraphy with [^{99m}Tc] pertechnetate showed no significant uptake in the right lobe and inhomogeneous activity in the left lobe (Fig. 1). No extra-thyroid lesions with increased [^{99m}Tc] pertechnetate uptake were found. Total-body scintigraphy with ^{99m}Tc-tetrofosmin (740 MBq i.v.; images obtained 30–120 min postinjection) was performed after the patient gave informed consent.

Faint tetrofosmin thyroid uptake was observed in the left lobe, while inhomogeneous activity was found in the right lobe (Fig. 2A). The two nodules clinically detected and described on US images had no significant tracer uptake. Extra-thyroid images detected five lesions with significant accumulation of tetrofosmin. A bilobate area of intense uptake was located in the cervical spine (Fig. 2B). Irregular increased uptake was also found in the dorsal spine where radiographs and CT showed abnormalities (Fig. 2B). Finally, three other lesions were detected in the chest (Fig. 2A, B). Early (30–60 min) and delayed (120 min) tetrofosmin images were comparable. Thyroid uptake of tetrofosmin in a normal health subject is shown in Figure 3A. Normal chest and abdominal tetrofosmin distribution are illustrated in Figure 3B.

The patient also underwent ^{99m}Tc-sestamibi (740 MBq i.v.; images obtained 15–120 min postinjection) total-body imaging as part of an ongoing research protocol in our laboratory. Sestamibi images were comparable to those of tetrofosmin. Radionuclide bone scanning, cervical CT associated with FNAB, chest radiography and CT were performed to further characterize the lesions observed on the tetrofosmin images. Technetium-99m-methylene diphosphonate (MDP) bone scanning demonstrated reduced uptake in the upper portion of the cervical spine (Fig. 4A). Increased but inhomogeneous uptake in the lower region of the dorsal spine was observed (Fig. 4B). The cervical CT study without contrast en-

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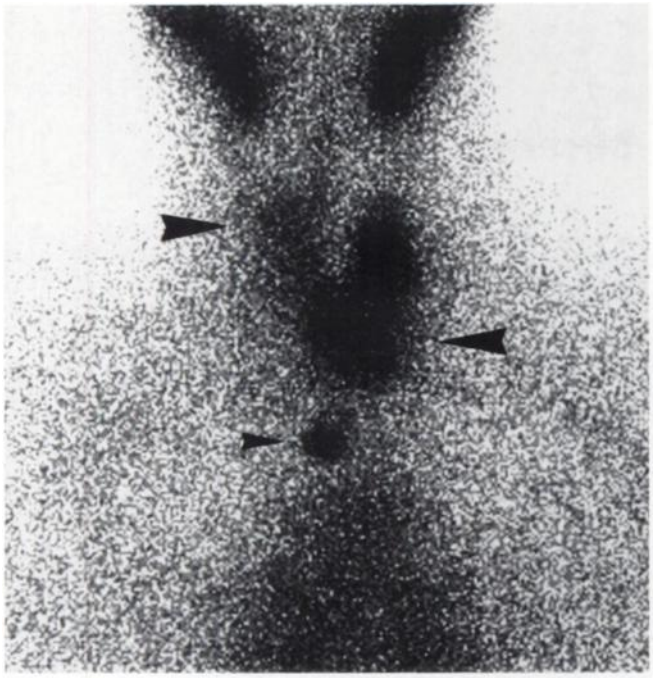

FIGURE 1. Technetium-99m-pertechnetate scintigraphy (anterior view) depicts no significant uptake in the right lobe; there is faint visualization of the upper pole of this lobe (arrow). Reduced activity in the nodule located in the inferior pole of the left lobe (arrow). A radioactive marker is located in the jugular region (small arrow).

hancement showed a large (6 cm) inhomogeneous bilobate lesion in the upper portion of the cervical spine (Fig. 5). FNAB findings documented a metastatic lesion by well-differentiated follicular thyroid adenocarcinoma. This lesion involved regional soft tissues with only adjacent bone erosion. The chest radiograph demonstrated a clear abnormality in the left lower hemithorax (Fig. 6), but the two foci of faint uptake, depicted in the lungs on the tetrofosmin images, were not identified. Chest CT confirmed the lesion in the left lower hemithorax and showed two nodules in the lungs, one for each. Similarly, the lesion of the left lower chest wall consisted of regional soft-tissue abnormalities without bone involvement.

The patient underwent total thyroidectomy and a follicular-papillary (mixed) thyroid adenocarcinoma was histologically documented. In particular, the left lobe lesion was characterized by the presence of calcification and blood. The right lobe lesion was cystic with associated calcification. The tumor was invasive and not capsulated with vascular tumor emboli. One month after surgery, the patient underwent serum thyroglobulin assay, which measured 153 ng/ml, and ^{131}I total-body scanning, which showed intense radionuclide abnormal uptake in all extra-thyroidal tumor lesions previously described. Therefore, ^{131}I therapy (100 mCi) was performed to treat tumor metastases.

DISCUSSION

Different tracers are used in the evaluation of patients with thyroid cancer (*5–7*). Thallium-201 has been used in the evaluation of clinically suspicious primary nodules or during postsurgical follow-up, particularly in those patients with tumor lesions not iodine-avid (*8–11*). Thallium, is not ideal, however, for radionuclide imaging, and ^{99m}Tc-labeled compounds have been proposed to circumvent this limitation. Our preliminary results demonstrated that ^{99m}Tc-V-DMSA may be concentrated in primary and metastatic sites of differentiated thyroid carcinomas (*12*). These findings suggest that DMSA allows better characterization of primary malignant thyroid nodules compared to [^{99m}Tc]pertechnetate scintigraphy and it is more sensitive than ^{131}I in the evaluation of metastases (*12*). We recently described ^{99m}Tc-V-DMSA uptake in a patient with thyroid involvement by histiocytosis X (*13*). Sestamibi, a lipophilic radiopharmaceutical, has been proposed for evaluation of thyroid abnormalities such as functional and neoplastic disorders (*14–19*).

Tetrofosmin is a new lipophilic technetium-phosphine agent proposed initially for myocardial perfusion imaging (*2*). The precise mechanism of tetrofosmin uptake into myocardial cells is not well known, but it is likely to be similar to that of sestamibi (*2*). Preliminary experimental data demonstrated that tetrofosmin accumulates in the mitochondria, phenomenon dependent on the amount of proteins and energetic substrate (*20*). In this report, we used tetrofosmin with our patient since we hypothesized that its biological features and intracellular uptake mechanisms could justify its clinical applications in neoplastic diseases.

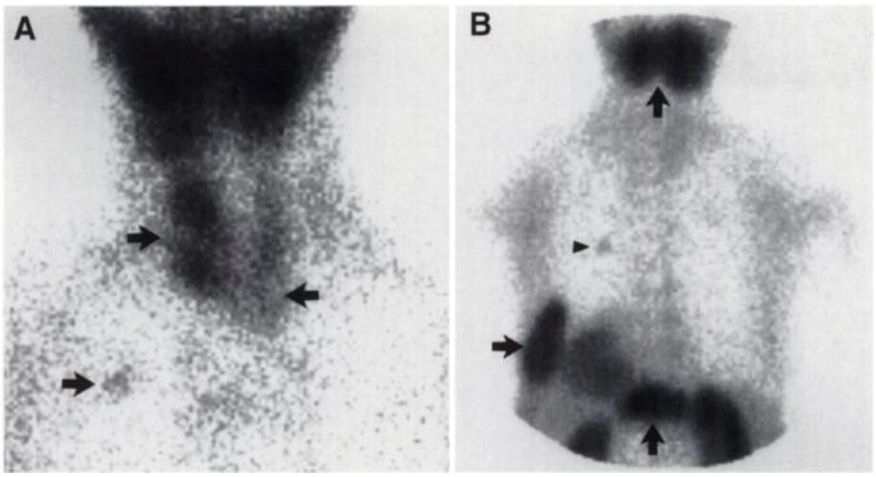

FIGURE 2. Technetium-99m-tetrofosmin scintigraphy. (A) Anterior view shows no significant uptake in the thyroid nodules (arrows), but there is a focus of abnormal uptake in the upper right hemithorax (arrow). (B) Chest and abdomen posterior view shows abnormal uptake in cervical and dorsal spine and in the left hemithorax (arrows). There is normal tracer distribution in the myocardium, superior pole of the kidneys.

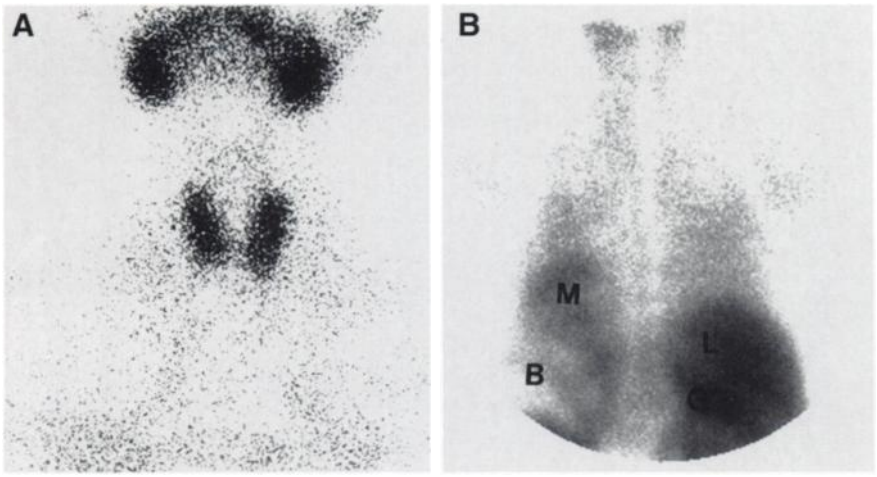

FIGURE 3. Technetium-99m-tetrofosmin imaging in a normal subject. (A) Neck anterior view shows normal tracer distribution in the thyroid, with physiological uptake in the salivary glands. (B) Chest and abdomen posterior view shows physiological tracer distribution in the myocardium (M), liver (L) and gallbladder (G). Inhomogeneous activity in the bowel (B). Diffuse and mild activity in the lungs, with photon attenuation in the spine.

In particular, the physiological characteristics of this tracer, which rapidly clears from normal thyroid tissue, suggest that it may be retained longer in malignant tumor lesions.

In our patient, tetrofosmin imaging clearly detected multiple metastatic lesions in the spine and chest as well as increased abnormal uptake in tumor sites. Sestamibi imaging showed comparable results. These tumor lesions were then confirmed using morphologic imaging modalities and/or FNAB. No increased tetrofosmin and sestamibi uptake were observed in the thyroid nodules. This latter finding may be explained by the fact that goiter changes mainly occur in such lesions (*18*). The association of thyroid cancer and goiter abnormalities observed in this study has been widely described and is not surprising (*21*). We compared tetrofosmin and ^{201}Tl images in this study. The labeling of this tracer with ^{99m}Tc, however, represents a significant advantage for scintigraphic imaging compared to ^{201}Tl. Thus, ^{99m}Tc-tetrofosmin total-body scintigraphy accurately staged thyroid tumors.

In patients with differentiated thyroid tumors, the most frequent sites of metastases are lymph nodes, lungs and bones (*22*). In our patient, unusual metastatic lesions occurred in the soft tissues of the chest wall and cervical spine. These findings were documented by integrated, but discordant imaging results. CT images showed soft-tissue abnormalities in these anatomic regions, but corresponding increased ^{99m}Tc MDP was not observed. Conversely, abnormal tetrofosmin uptake was found.

CONCLUSION

In a patient with well-differentiated mixed thyroid carcinoma, tetrofosmin total-body scintigraphy detected unusual metastatic lesions. Therefore, this radionuclide technique may be useful in patients with thyroid cancer. Further in vitro and clinical studies are needed to assess tetrofosmin's role in the evaluation of thyroid tumors.

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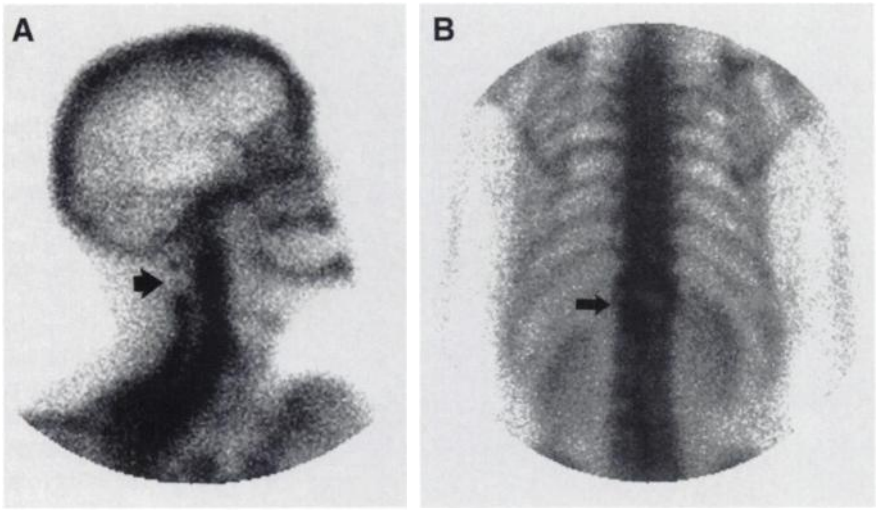

FIGURE 4. Technetium-99m-MDP bone scan. (A) Right lateral view of the cervical spine and skull shows reduced activity in the cervical spine (arrow). (B) Posterior view of the spine shows increased but inhomogeneous uptake in the dorsal spine (arrow).

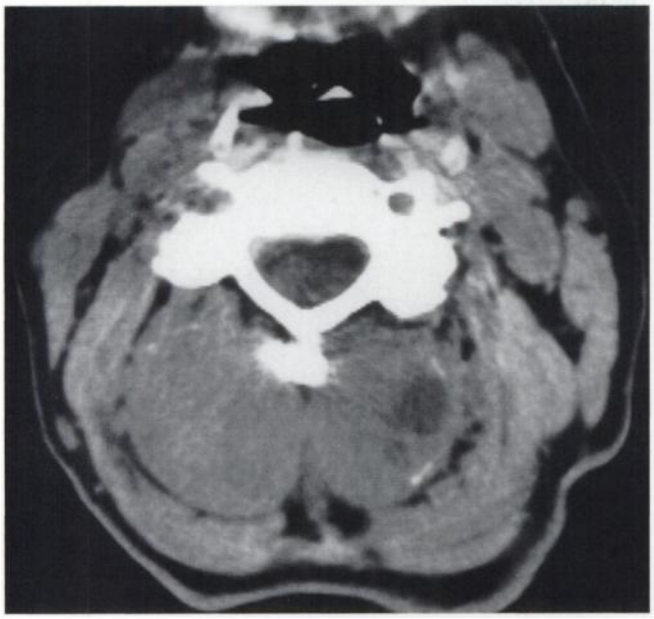

FIGURE 5. Cervical CT scan (axial view): large bilobate heterogeneous lesion.

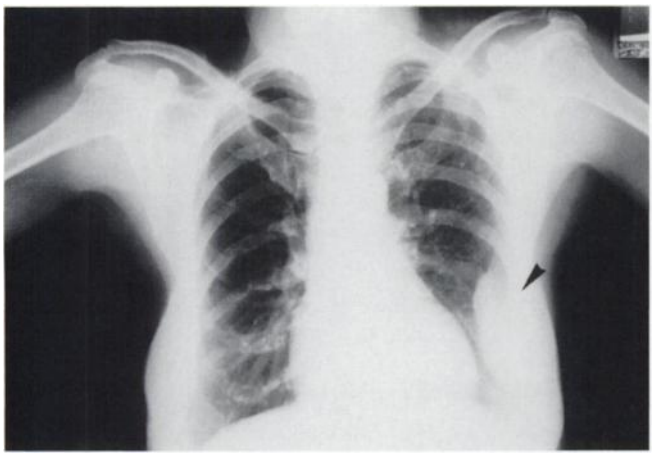

FIGURE 6. Chest radiograph depicts an abnormality in the left lower hemithorax (arrow). The two foci of faint ^{99m}Tc-tetrofosmin uptake in the lungs were not identified.

REFERENCES

1. Higley B, Smith FW, Smith T, et al. Technetium-99m-1,2-bis [bis (2-ethoxyethyl) phosphino] ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J Nucl Med* 1993;34:30–38.
2. Jones S, Hendel RC. Technetium-99m tetrofosmin: a new myocardial perfusion agent. *J Nucl Med Technol* 1993;21:191–195.
3. Oster ZH, Strauss HW, Harrison K, Burns HD, Pitt B. Thallium-201 distribution in the thyroid: relationship to thyroidal trapping function. *Radiology* 1978;126:733–734.
4. Civelek AC, Durski K, Shafique I, et al. Failure of perchlorate to inhibit Tc-99m isonitrile binding by the thyroid during myocardial perfusion studies. *Clin Nucl Med* 1991;16:358–361.
5. Clarke SEM. Radionuclide imaging in thyroid cancer. *Diagnostic Imaging* 1991;30:43–52.
6. Piwnica-Worms D, Holman BL. Noncardiac applications of hexakis-(alkylisonitrile) technetium-99m complexex. *J Nucl Med* 1990;31:1166–1167.
7. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with In-111-DTPA-Phe and I-123-Tyr-octreotide: the Rotterdam experience with more that 1000 patients. *Eur J Nucl Med* 1993;20:716–731.
8. Ochi H, Sawa H, Fukuda T, et al. Thallium-201 chloride thyroid scintigraphy to evaluate benign and/or malignant nodules. *Cancer* 1982;50:236–240.
9. El-Desouki M. Thallium-201 thyroid imaging in differentiating benign from malignant thyroid nodules. *Clin Nucl Med* 1991;16:425–430.
10. Hardoff R, Baron E, Sheinfeld M. Early and late lesion-to-nonlesion ratio of thallium-201-chloride uptake in the evaluation of "cold" thyroid nodules. *J Nucl Med* 1991;32:1873–1876.
11. Ramanna L, Waxman A, Braunstein G. Thallium-201 in differentiated thyroid cancer: comparison with radioiodine scintigraphy and serum thyroglobulin determinations. *J Nucl Med* 1991;32:441–446.
12. Lastoria S, Vergara E, Varrella P, et al. Imaging of differentiated thyroid tumors with Tc-99m (V)DMSA [Abstract]. *J Nucl Med* 1993;34:12P.
13. Maurea S, Lastoria S, Klain M, et al. Diagnostic evaluation of thyroid involvement by histiocytosis X. *J Nucl Med* 1994;35:263–265.
14. Kao C-H, Wang S-J, Liao S-Q, Lin W-Y, Hsu C-Y. Quick diagnosis of hyperthyroidism with semiquantitative 30-min technetium-99m-methoxy-isobutyl-isonitrile thyroid uptake. *J Nucl Med* 1993;34:71–74.
15. O'Driscoll CM, Baker F, Casey MJ, Duffy GJ. Localization of recurrent medullary thyroid carcinoma with technetium-99m-methoxyisobutylisonitrile scintigraphy: a case report. *J Nucl Med* 1991;32:2281–2283.
16. Balon HR, Fink-Bennett D, Stoffer SS. Technetium-99m-sestamibi uptake by recurrent Hurthle cell carcinoma of the thyroid. *J Nucl Med* 1992;33:1393–1395.
17. Scott AM, Kostakoglu L, O'Brien JP, Strauss DJ, Abdel-Dayem HM, Larson SM. Comparison of technetium-99m-MIBI and thallium-201-chloride uptake in primary thyroid lymphoma. *J Nucl Med* 1992;33:1396–1398.
18. Maurea S, Lastoria S, Klain M, et al. Technetium-99m MIBI scan in the initial evaluation and post-surgical follow-up of thyroid cancer [Abstract]. *J Nucl Med* 1994;35:166P.
19. Yen TC, Lin HD, Lee CH, Chang SL, Yeh SH. The role of technetium-99m sestamibi whole-body scans in diagnosing metastatic Hurthle cell carcinoma of the thyroid gland after total thyroidectomy: a comparison with iodine-131 and thallium-201 whole-body scans. *Eur J Nucl Med* 1994;21:980–983.
20. Songadele JA, Younes A, Maublant J, Veyre A, Platts EA, Pickett RD. Uptake of Tc-99m tetrofosmin in isolated mitochondria: evidence for an active mechanism [Abstract]. *J Nucl Med* 1994;35:46P–47P.
21. Beierwaltes WH. Endocrine imaging in the management of goiter and thyroid nodules: part I. *J Nucl Med* 1991;32:1455–1461.
22. Norton JA, Doppman JL, Jensen RT. Cancer of endocrine system. In: De Vita VT, Hellman S, Rosenberg SA, eds. *Principals and practice of oncology. Cancer.* Philadelphia: J.B. Lippincott; 1989:1269–1285.