Comparison of ^{99m}Tc(V)-DMSA with ^{99m}Tc-EDDA/HYNIC-Tyr³-octreotide scintigraphy in the detection of medullary thyroid tumor foci in a patient with elevated level of calcitonin after surgery: a case report

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ABSTRACT

Background: Technetium-99m pentavalent dimercaptosuccinic acid [99mTc(V)-DMSA] scintigraphy exhibits a crucial role in the preoperative assessment of residual or recurrent medullary thyroid carcinoma (MTC).

Case Presentation: 99mTc(V)-DMSA scintigraphy was performed in a patient with histopathologically proven MTC expressing a high level of calcitonin using a locally formulated kit. Marked uptake of the radiotracer was observed by the locally metastatic foci. The same patient was then subjected to somatostatin receptor scintigraphy (Octreoscan) and the results were found comparable. Both the scanning was completed within 24 hours with good quality images.

Conclusion: In-house preparation from renal DMSA kit, better resolution, good stability, and easy procedure with minimum cost make 99mTc(V)-DMSA a good imaging agent for visualization of MTC in the centers where 99mTc-ethylenediamine-N, N-diacetic acid/6-hydrazinonicotamide-3-carboxylic acid-Tyr³-octreotide is not available.

Keywords: Calcitonin, MTC, octreotide, radiochemical purity, ^{99m}Tc (V)-DMSA.

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Background

Medullary thyroid carcinoma (MTC) is an uncommon but challenging malignant tumor that arises from the parafollicular calcitonin-secreting cells of the thyroid [1]. Hence, elevated serum calcitonin level is a reliable marker for differentiated recurrent MTC. MTC accounts for 3%-10% of all thyroid cancers and 13.4% of all thyroid-related deaths [2]. According to the Oncology Registry record at our institute, there have been 59 cases of MTC in the last 10 years which comprises about 0.09% of all malignant cases registered in the hospital.

In time diagnosis, staging, and assessment of recurrence in MTC are of utmost importance for the proper management of the disease [3]. This tumor is resistant to external beam radiotherapy and shows poor response to chemotherapy. Hence, surgery is the only strategy for potential treatment [1,4,5]. However, for a successful surgical attempt, one should be familiar with site and extent of disease [6]. The conventional imaging techniques sometimes show negative results or have some limitations to be applied. Therefore, nuclear medicine techniques are sought to image, detect, or visualize MTC.

The various functional imaging tools commonly used for this purpose are: iodinated (123I) or (131I) metaiodobenzylguanidine (MIBG), Thallium chloride (201Tl), pentavalent 99mTc dimercaptosuccinic acid [99mTc(V)-DMSA], 111In and 99mTc labeled octreotide, ¹⁸F-fluorodeoxy glucose positron emission tomography (PET), monoclonal anti-carcinoembroyonic antigen labeled antibodies, and other PET tracers such as ¹⁸F-dihydroxyphenyl alanine and ⁶⁸Ga-1'4'7'10 tetraazacyclododecane-1'4'7'10-tetraacetic acid Tyr3-octreotide (DOTATOC) or ⁶⁸Ga-1'4'7'10-Tetraazacyclododecane-1'4'7'10-tetraacetic acid Tyr3-octreotate (DOTATATE) have shown encouraging results [7,8].

The availability, cost-effectiveness, and robust clinical application are considered as the crucial factors in the selection of a radiopharmaceutical [9]. In this perspective, ^{99m}Tc-labeled octreotide [^{99m}Tc-ethylenediamine-N, N-diacetic acid (EDDA) 6-hydrazinonicotamide-3-carboxylic acid (HYNIC) Tyr3-octreotide] scintigraphy is considered as one of the most appropriate methods for the diagnosis, staging, and assessment of treatment response in MTC, especially in lesions that express with

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somatostatin receptors [10]. Specifically, it has many advantages including fast clearance, easy labeling, rapid tissue penetration, and lesser time to scan the patient. In the clinical set up where patients flow is limited and clinical indications are few, the tracer is not always readily available at many institutes. Moreover, the relatively higher price also hinders its frequent use, particularly in a low socio-economic country like Pakistan, which ultimately delays the imaging procedures.

Alternatively, 99mTc(V)-DMSA has a crucial role in the pre-operative evaluation, assessment of residual disease or recurrence of MTC, and other related soft tissue tumors [9,11]. But now the use of this agent is going to be abandoned in most countries due to the introduction of newer alternatives like 68Ga-DOTATOC or 68Ga-DOTATATE. Albeit, 99mTc(V)-DMSA is considered as cost effective and time efficient, a comprehensive cohort of studies are essential to establish such and other favorable characteristics [6,12]. Previously published work from our institute also suggests 99mTc(V)-DMSA as a good tumor seeking agent for visualization of MTC and its involved lymph nodes in the mediastinum [6]. As 99mTc(V)-DMSA can be easily formulated from the renal DMSA kit and has comparable results with 99mTc-EDDA/HYNIC-Tyr3-octreotide (Tektrotyd), we successfully imaged a patient with MTC with locally formulated 99mTc(V)-DMSA and then, made its comparison with the results of 99mTc-EDDA/HYNIC-Tyr3-octreotide (Tektrotyd) scintigraphy for lesion detection sensitivities.

Case Presentation

A 35 years old male was diagnosed 1 year ago as a case of MTC after excision biopsy from neck swelling. He was referred to nuclear medicine department from oncology section for somatostatin receptor scintigraphy. At the time of presentation, his serum calcitonin level was 6,324 pg/ml (normal range is <8.4). However, due to non-availability of this radiopharmaceutical, it was decided to perform 99mTc(V)-DMSA scan for this patient. The radiopharmaceutical was locally prepared using renal DMSA kit, as previously described [6,9]. More specifically, the commercial DMSA kit supplied by Isotope Production Division, PINSTECH, Islamabad, Pakistan that contains 1 mg DMSA, 0.35 mg of SnCl₂ 2H₂O, 0.35 mg of ascorbic acid, and 20 mg of mannitol were taken and were mixed with 1 ml of 0.167 M sodium bicarbonate solution to make the medium alkaline. The pH of the reaction mixture was (8.4-8.5) determined by pH indicator strips. Then 20 mCi (740 MBq) of freshly eluted sodium pertechnetate (Na99mTcO₄) from Mo99/ Tc99m generator was added to the vial. The vial was incubated for 15 minutes at room temperature for reaction to complete. Quality control tests were carried out by thin-layer chromatography and the radiochemical purity was found to be 95.6% \pm 0.5%. The whole process was carried out under aseptic condition.

The radiopharmaceutical was then injected into the median cubital vein of the patient through an indwelling IV cannula. Early 1 hour [Figure 1 (a,b)] and delayed 24 hours (Figure 1c) anterior spot images of the cervico-thoracic region and abdomen were acquired using Siemens Orbitor gamma camera with low energy all purpose collimator and energy window of 15% centered at 140 KeV photopeak.

After 1 month of the 99m Tc(V)-DMSA scan, the same patient underwent 99m Tc-EDDA/HYNIC-Tyr³-octreotide scintigraphy. The cold kit (brand name: Tektrotyd) was obtained from PARS, Isotope Company, Iran. The kit was reconstituted with 30 mCi (1,110 MBq) of 99m Tc and the labeling yield was found at 98.2% \pm 0.2%. Then, 20 mCi (740 MBq) of the radiopharmaceutical was slowly injected into the median cubital vein. Whole body imaging was performed on the same institutional protocols after 2 and 4 hours post injection [Figure 2 (a,b)].

All the images were compared and interpreted by the nuclear physician in view of the clinical presentation of the patient. The images were very sharp with excellent resolution and the lesion detection potentials were common in both the cases. Marked uptake of both the radiotracer was



Figure 1. Illustrative 99mTc(V)-DMSA scintigraphy images; (a) 1-hour post injection image of the anterior head and neck region, (b) 1-hour post injection image of the anterior thoracic region, and (c) 24-hour post injection image of the anterior chest region.



Figure 2. (a) Two and (b) four hour post injection illustrative whole body imaging of 99mTc-EDDA/HYNIC-Tyr3-octreotide scan.

seen in four foci of the neck thoracic region and showed good radiotracers avidity by the lesions. The number of lesions detected by the ^{99m}Tc(V)-DMSA on the initial scan in the neck and thorax region were found to be the same as detected later by ^{99m}Tc-EDDA/HYNIC-Tyr³-octreotide scintigraphy. No additional focus was detected by the Octreoscan. The 24-hour post-injection images were additionally acquired to see the redistribution of the tracers over a long period of time. It may be noted that the Ethical Committee of The Institute approved this study for publication.

Discussion

MTC is a rare neuroendocrine tumor and octreotide scan is considered as a specific imaging agent for detection of primary and metastatic MTC with higher sensitivity than ^{99m}Tc tetrofosmin and ²⁰¹Tl scintigraphy [13]. Somatostatin receptor scintigraphy is used to detect the primary tumor focus for staging, the decision of therapy protocol, and evaluation of therapy response in neuroendocrine tumors and other related cancers [14]. It has proved to be better than other diagnostic tools for the detection of cervical and mediastinal lymph node metastases in MTC or other somatostatin receptor-positive tumors [15]. Several studies support that the sensitivity and specificity of Octreoscan are higher than that of 99mTc (V)-DMSA in the work up of MTC. However, limitations are associated with this radiotracer like availability and high prices. In most developing and under developed countries, it is imported from other developed countries and patients have to wait for a prolonged duration. Patient's affordability is another major hurdle in its routine use. In such conditions, ^{99m}Tc (V)-DMSA scanning is an affordable and a reasonably sensitive imaging agent for localization of recurrent or metastatic disease.

^{99m}Tc (V)-DMSA is a non specific multifunctional imaging agent that commonly accumulates in MTC [12]. Its role in the evaluation of MTC has already been compared with other functional imaging tools like ¹³¹I MIBG, ^{99m}Tc tetrofosmin, ²⁰¹Tl scintigraphy, etc [13]. ^{99m}Tc (V)-DMSA plays a crucial role in the assessment of residual tumor or metastatic disease in patients with medullary thyroid cancer, especially with high postoperative calcitonin levels. The ease of preparation of ^{99m}Tc (V)-DMSA and good imaging characteristics of the radiopharmaceutical make it an alternative imaging tool in patients having proven MCT [6,9].

MTC is an uncommon NET and patients are neither readily available nor always compliant for the tedious procedures of research. Nevertheless, our experience of avid and persistent ^{99m}Tc (V)-DMSA uptake in all the tumor deposits in the thoracic region has encouraged us to explore its potentials where EDDA/HYNIC-Tyr³octreotide and ⁶⁸Ga-DOTATOC or ⁶⁸Ga-DOTATATE are not available. Moreover, ^{99m}Tc (V)-DMSA shows low uptake in the liver and spleen as compared to octreotide scan, hence, the uptake in these regions will be clearly appreciated where it will be overshadowed with octreotide. The prolonged residence of the of ^{99m}Tc (V)-DMSA can also be utilized for an alternate therapeutic option when tagged with β -emitting radionuclides like ¹⁸⁸Re, ¹⁸⁶Re, and others.

Conclusion

Locally formulated ^{99m}Tc (V)-DMSA scintigraphy is an easy, economical, and promising imaging modality in MTC patients with high levels of calcitonin. In comparison with ^{99m}Tc-EDDA/HYNIC-Tyr³-octreotide scintigraphy, its availability and application is easier. It can be used as an alternative imaging method when ^{99m}Tc-EDDA/HYNIC-Tyr³-octreotide and ⁶⁸Ga-DOTATOC or ⁶⁸Ga-DOTATATE are not available.

Acknowledgement

None

List of abbreviations

^{99m} Tc(V)-DMSA	Technetium-99m pentavalent dimercaptosuc-	
	cinic acid	
MTC	Medullary thyroid carcinoma	
PET	Positron emission tomography	

Consent for publication

Written Informed Consent was taken from the participants of the study.

Ethical approval

Ethical Committee of The Institute approved this study for publication.

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Summary of the case

Patient (gender, age)	1	Male, 35 years
Final Diagnosis	2	MTC on fine needle aspiration cytology of anterior neck swelling, Thyroidectomy with level II lymph nodes dissection
Symptoms	3	Chest tightness, dyspnoea
Medications (generic)	4	Post surgery has not been started on any treatment
Clinical Procedure	5	Blood chemistry investigation (substantially raised serum calcitonin level), magnetic resonance imaging, computed tomography scan
Specialty	6	Thyroid clinic, nuclear medicine