

⁹⁹MTC-MIBI USE AS A NON-SPECIFIC TUMOUR MARKER IN THE DIAGNOSIS OF BRAIN METASTASES OF UNKNOWN PRIMARY MALIGNANT ETIOLOGY

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ABSTRACT

Tumours of unknown etiology are a heterogeneous group of malignancies whose first presentation is a metastatic disease and the primary neoplasm site remains not detected by the time of initial diagnosis. Brain is a relatively common localization for metastases from various malignancies, mainly from lung, melanoma, kidney, etc. In certain cases, however, the primary tumour site could not be diagnosed by routine tests and additional methods are utilized in attempt to localize it. We aimed at evaluating the use of ^{99m}Tc-MIBI as a non-specific tumour marker in patients with brain metastases and unknown primary tumour site. The study covered 11 patients with brain metastases but without any evidence of primary tumour according to the routine diagnostic tests. A single i.v. dose of 20 mCi ^{99m}Tc-MIBI was used as a non-specific tumour marker. All the patients underwent the following examinations: dynamic perfusion study of the abdomen, scintimammography (females), SPECT of thorax, whole body scan, and brain SPECT performed consecutively by means of Diacam Siemens gamma camera. Two patients showed a pathologic MIBI uptake in the lung morphologically proven to be non-small cell lung cancer (NSCLC). Lesions were evident on SPECT only. One patient demonstrated MIBI uptake in the axillary lymph nodes, however, no primary tumour site was verified thereafter. The remaining 8 patients did not show any foci of abnormal MIBI uptake consistent with the primary tumour or extracranial metastases. Usage of ^{99m}Tc-MIBI as a non-specific tumour marker could be of value for detecting the primary tumour site in case of brain metastases of unknown etiology.

Key words: ^{99m}Tc-MIBI, brain metastases, tumour of unknown etiology, diagnosis, SPECT

INTRODUCTION

Tumour (cancer) of unknown primary etiology (TUP, CUP) is defined as a histologically proven metastatic lesion when the primary tumour site is not localized prior to therapy. This specific group accounts for about 5-10% of any diagnosed malignancies (4,5). Detecting the primary tumour site is not always achieved despite the extensive application of routine methods. Furthermore, primary tumour site remains unrevealed in 20-50% of the patients even at post-mortem exploration (1,3,6,7). The most common histological types of TUP and CUP are adenocarcinoma, low differentiated carcinoma, squamous cell carcinoma, neuroendocrine tumours with liver, lung, bones and lymph nodes being the most common metastatic localizations. Brain is relatively rarely affected and because of the specificities of the location and the related symptoms, the final diagnosis and decision making has to be done in

shorter terms. Symptoms like headache or epilepsy are commonly the first alarm that leads the patient to the physician as neurologists and/or neurosurgeons being the first contact specialists. Prognosis is, generally, poor and detection of primary tumour site is of great importance for further treatment strategies. Detecting the primary tumour localization of the malignant disease includes a wide spectrum of diagnostic modalities such as imaging methods, laboratory testing, endoscopy etc., which, however, in some cases fail to reveal the primary site. Based on this suboptimal yield of the conventional methods any diagnostic procedure that could establish diagnosis other than TUP is justified. Positron emission tomography with ¹⁸F-FDG and, recently, FDG PET/CT is one of the most powerful modalities for detecting the primary tumour site, significantly reducing the number of patients referred as TUP (2). Unfortunately, despite its diagnostic yield in these patients FDG PET is not widely available and is comparatively more expensive than the routine imaging modalities including SPECT with non-specific tumour markers such as ²⁰¹TlCl, ^{99m}Tc MIBI, and Tetrofosmin.

Based on the literature data about the usage of nuclear medicine methods, namely gamma camera scintigraphy with non-specific tumour-seeking agents in patients with various

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brain tumours as diagnostic procedures in lung cancer, breast cancer, thyroid cancer, we precluded the method could be of value in patients with brain metastases and unknown primary tumour site, probably, following the routine diagnostic examinations if negative and prior to FDG PET if available and/or affordable.

The aim of this study was to evaluate whether ⁹⁹mTc-MIBI used as a non-specific tumour marker could be capable of revealing the primary tumour localization in the patients with brain metastases of tumours of unknown etiology.

MATERIAL AND METHODS

The study covered 11 patients, 5 males and 6 females with brain metastases of unknown primary tumour site (Table 1). Two patients were preoperatively examined with subsequent histological verification after the brain surgery. The rest patients presented postoperatively with already known metastatic tumour histology. All the patients had been extensively examined by means of imaging and laboratory methods prior to be referred to nuclear medicine examination. There was a consensus diagnosis of brain metastases of TUP in all the cases. Despite the established diagnosis from the referring hospital we included only the patients having as a minimum at least x-ray or CT of the thorax, mammography (women), ultrasound or CT scan of the abdomen and pelvis and thyroid ultrasound for the patient with papillary cancer histology. Results from the endoscopic (gastroscopy or colonoscopy) examinations were not obligatory demanded because of the expected low sensitivity for gastrointestinal tumours of scintigraphy used.

All the patients underwent scintigraphic evaluation with anon-specific tumour marker ⁹⁹mTc MIBI using a combined protocol which consisted of early dynamic (perfusion) scintigraphy of the abdominal region, scintimammography, SPECT of the thorax, whole body scan (WBS) and brain SPECT performed after the intravenous administration of a single 20 mCi dose of ⁹⁹mTc MIBI. Acquisitions started since the time of administration onwards up to two hours after injection and included protocols typical of the particular region scanned (breasts, lung). This was possible thanks to the wide scanning interval after the administration in which the tumour activity could be detected. Use was made of Dixacam Siemens single-headed SPECT gamma camera equipped with low-energy general purpose (LEAP) and low-energy high resolution (LEHR) collimators, depending on the acquisition set, energy window centered at 140 KeV, and 15% window width. Dynamic perfusion examination of the abdomen was performed as a dual phase study consisting of vascular phase (2 frames by 60 sec.) and blood pool phase (3 frames by 60 sec.) using visual analysis only. Scintimammography (SMG in females only) was done 15 min. after administration using standard protocol. Results were visually assessed.

Thorax SPECT (TxSPECT) was performed after SMG using LEHR collimator, 360° circular orbit, Step-and-Shoot

mode, 64 frames of 30 sec. each, 64X64 matrix, reconstruction by FBP, Low pass (Butterworth filter) and visual analysis only. Whole body scan with anterior and posterior view was applied after TxSPECT with scan speed of 20 cm/min., 1024x256 matrix.

Brain SPECT was performed finally (up to 120 min after administration of 20 mCi ⁹⁹mTc-MIBI, using LEHR collimator, 360° circular orbit, 64x64 matrix, Step-and-Shoot mode, 64 projections, 25 sec. each, FBP (filtered back projection) Reconstruction, Low pass filter (Butterworth), attenuation correction (Chang, 0,12) and visual/semiquantitative analysis.

Table 1 shows the histological types as defined from the brain metastases after neurosurgery (Table 1).

Table 1. Histology types as defined from the brain metastases after neurosurgery

No	Histology	Time of testing
1	Low differentiated spinocellular	pre/postoperatively
2	Low differentiated carcinoma	postoperatively
3	Low differentiated adenocarcinoma	postoperatively
4	Low differentiated adenocarcinoma	postoperatively
5	Adenocarcinoma	postoperatively
6	Low differentiated carcinoma	preoperatively
7	Low differentiated carcinoma	postoperatively
8	Clear cell carcinoma	postoperatively
9	Small cell cancer	postoperatively
10	Papillary cancer	postoperatively
11	Low differentiated spinocellular	postoperatively

RESULTS AND DISCUSSION

Biodistributions of the non-specific tumour marker for SPECT, namely ²⁰¹TlCl, Tetrofosmin and MIBI are similar and characterized by high abdominal activity due to liver and bile being the primary excretion route. This virtually excludes the radiopharmaceuticals of this type as a reliable diagnostic tool for the detection of sub-diaphragmatic/abdominal tumour activity. Despite this obvious limitation we included early dynamic acquisition of the abdomen in our combined protocol as representative of blood pool only and perfusion of this region presuming that higher tumour vascularization would be prominent above the usual normal tissue background perfusion. Detection of hypervascular abdominal tumours in the early flow (0-60/120 min.) and pool phase is well-known as an additional finding in other nuclear medicine studies using non-tumour markers (such as MDP and DTPA). None of our patients studied by this protocol showed any similar patterns suggestive of intraabdominal malignancy. Despite the negative findings in our series we believe that this part

of the acquisition should not be discarded, at least because of the theoretical yield and as it is not resulting in higher radiation burden to the patient.

All the female patients underwent scintimammography 15 min. after the administration of 20 mCi ^{99m}Tc MIBI. None of patients' images were read as positive (defined as focal or highly diffuse breast uptake). In one patient (No 3) a focal uptake in the axilla was observed (already known metastatic site, apart from the brain metastases), however, there was no pathologic uptake in the mammary glands. The same patient had no breast abnormalities on previously performed mammography and breast ultrasound examination. In two patients thorax SPECT revealed well-defined foci of high MIBI uptake in the lungs, i. e. in the right hilus (patient No 1) (Fig. 1) and in the right costo-diaphragmatic sinus (patient No 2). The first patient was so far three times operated for brain metastases and underwent contrast-enhanced CT scans of the thorax, the latter performed 6 months before the nuclear medicine procedure. All of them were negative for a tumour, probably, due to its smaller size and hilar location.

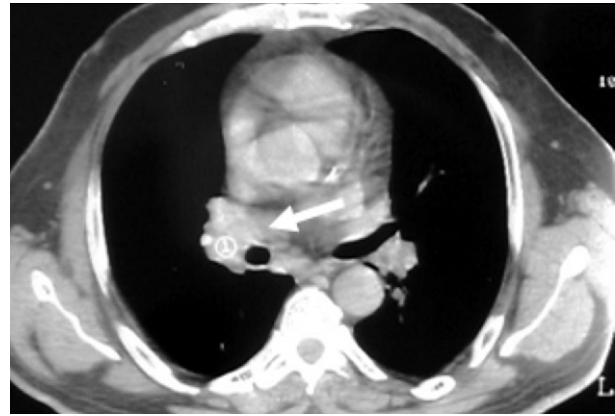


Fig. 2. Postscintigraphic CT scan - a mass in the right hilus later proved to be NSCLC

The late brain SPECT performed in all the patients was in complete concordance with the results of the CT and/or MRI. All the known metastatic lesions above 10 mm were

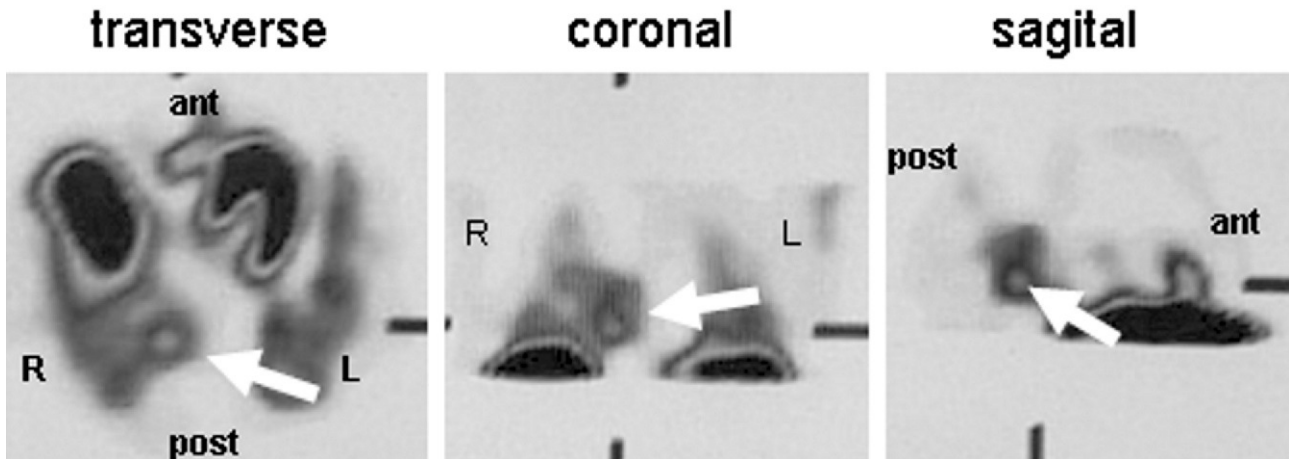


Fig. 1. Thorax SPECT of patient No 1 - a clearly defined focus of pathologic uptake in the inferior part of right hilus

The follow-up CT scan after the scintigraphy revealed an enlarging hilar mass located at the site of high MIBI uptake and later diagnosed as a non-small cell lung cancer (NSCLC) (Fig. 2). In patient No 2, only a plain chest X-ray was performed and considered normal. The follow-up control CT scan revealed a well-defined lung tumour in the right lower lobe later on confirmed as NSCLC. In this case the tumour location just behind the liver is a probable reason for the failed recognition of the disease on plain x-ray.

In patient No 3, by means of thorax SPECT an accumulation in the right axilla was established as an already known metastatic site, however, there were no other changes typical of a primary tumour. Rest patients did not present with any abnormalities on thoracic SPECT.

WBS did not demonstrate any pathologic uptake in all the patients, except for patient No 3 in whom the axillary uptake was faintly visualized, and patient No 1, in whom the focal hilar lesion detected of SPECT was questionable but definitely inconclusive without the SPECT data.

clearly visualized as foci of high MIBI uptake - in one patient preoperatively as a solitary metastasis and in three patients postoperatively, at sites of known but unresected metastases, or of newly-found ones. In one patient there is a falsely positive scintigraphic result later on clarified after comparison with MRI to be due to postoperative lateral traction of the choroid plexus as a usual site for physiologic MIBI accumulation. MIBI brain SPECT was negative for metastases in the rest patients without any evidence of new or persistent metastases on CT and/of MRI. The results from all the nuclear medicine tests are demonstrated in Table 2.

CONCLUSION

^{99m}Tc -MIBI used as a non-specific tumour marker can be of value for detecting the primary tumour site in case of brain metastases of unknown etiology. The actual role of the test is, however, not defined yet. Its application should,

Table 2. Results from the combined scintigraphic protocol with ^{99m}Tc MIBI in patients with brain metastases and TUP

No	Histology	Time of testing	Perfusion abdomen	SMG	SPECT thorax	WBS	SPECT brain	Final diagnosis
1	Low differentiated spinocellular	pre/postoperatively	-	N/A	+	±	+	NSCLC
2	Low differentiated carcinoma	postoperatively	-	-	+	-	-	NSCLC
3	Low differentiated adenocarcinoma	postoperatively	-	-	+	±	+	CUP
4	Low differentiated adenocarcinoma	postoperatively	-	-	-	-	-	CUP
5	Adenocarcinoma	postoperatively	-	-	-	-	+	CUP
6	Low differentiated carcinoma	preoperatively	-	-	-	-	+	CUP
7	Low differentiated carcinoma	postoperatively	-	-	-	-	-	CUP
8	Clear cell carcinoma	postoperatively	-	N/A	-	-	-	CUP
9	Small cell cancer	postoperatively	-	N/A	-	-	-	CUP
10	Papillary cancer	postoperatively	-	N/A	-	-	-	CUP
11	Low differentiated spinocellular	postoperatively	-	N/A	-	-	-	CUP

SMG - scintimammography; WBS - whole body scan; NSCLC - non-small cell lung cancer; TUP - tumour of unknown primary site; CUP - cancer of unknown primary site; N/A - not available

however, follow the conventional imaging if proved negative and precede FDG-PET if the latter is hardly available/affordable. Although it does not possess the sensitivity and specificity of a stand-alone test, it should be recommended for specifying the diagnosis in any SPECT-positive patients.

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