ORIGINAL

Technetium-99m sestamibi single photon emission computed tomography findings correlated with P-glycoprotein expression in pituitary adenoma.

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Abstract: The aim of this study is to evaluate whether the technetium-99m sestamibi (^{99m}Tc-MIBI) single photon emission computed tomography (SPECT) characteristics of pituitary adenomas might be correlated with cavernous sinus invasion, proliferative potential or the multidrug-resistance (MDR-1) gene product P-glycoprotein (Pgp) expression in pituitary adenomas. Fifteen patients with pituitary adenomas, including 10 nonfunctioning adenomas, two prolactinomas, two GH producing adenomas, and one ACTH producing adenomas was investigated for this study. SPECT images with ^{99m}Tc-MIBI were acquired 15 minutes (early) and 3 hours (delayed) after injection. The tumor-to-normal brain ratio was calculated both early (ER) and delayed (DR) images. Retention index (RI) was calculated using the following formula: (DR-ER)/ER×100%. The pituitary adenomas specimens were examined by immunohistochemistry using anti-Pgp and MIB-1 monoclonal antibodies.

^{99m}Tc-MIBI SPECT findings were not related to MIB-1 labeling index or cavernous sinus invasion. ^{99m}Tc-MIBI SPECT RI (-38.55±20.77) of the Pgp-positive group was significantly lower than that (-15.78±19.40) of Pgp-negative group (p=0.0494). No siginificant difference was observed in the ER and DR of ^{99m}Tc-MIBI SPECT between Pgp-positive and negative groups.

Our study suggests that although ^{99m}Tc-MIBI SPECT is not useful to evaluate the proliferative potential or cavernous sinus invasion of pituitary adenomas. ^{99m}Tc-MIBI SPECT could predict anti-cancer drug resistance related to the expression of Pgp in pituitary adenomas. J. Med. Invest. 53 : 285-291, August, 2006

Keywords : *MIBI-SPECT, pituitary adenoma, P-glycoprotein, Proliferative potential*

INTRODUCTION

Pituitary adenomas are generally considered as benign tumors, however about 30% of them behave aggressively such as cavernous sinus invasion (1-3). In such case, the tumor recurrence may be seen in a short period after operation, therefore, prediction of biologic behavior is important for therapeutic planning of this tumor. ^{201}Tl chrolide (^{201}Tl-Cl) single-photon emission computed tomography (SPECT) has been reported to be useful to detect tumor viability in malignant tumors (4, 5). Nakano *et al*. (6) demonstrated that invasive pituitary adenomas exhibited higher ^{201}Tl-Cl uptake indices on both the early and the delayed images, and that ^{201}Tl-Cl

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uptake index on delayed image correlated with MIB-1 labeling index (LI) in pituitary adenomas.

Technetium-99m sestamibi (^{99m}Tc-MIBI) have been considered a potential tumor imaging agent for detecting various kinds of cancer including brain tumor. Several investigators demonstrated that ^{99m}Tc-MIBI uptake correlated with histological malignancy or proliferative potential in gliomas (7-9). In addition, P-glycoprotein (Pgp), which is encoded by mutidrug resistance gene 1 (MDR1), recognizes certain chemotherapeutic agents as a substrate and prevents accumulation of some lipophilic cationic radiopharmaceuticals such as ^{99m}Tc-MIBI (10-14). Retention of ^{99m}Tc-MIBI is reduced in cells with a multidrug-resistant phenotype because of increased expression of the energy-dependent Pgp efflux pump, which expels the substrates from the cell (9, 12). Previous studies have shown an inverse relationship between the levels of Pgp and the balance of ^{99m}Tc-MIBI uptake and washout rates in tumor cells (9, 10, 12). However, little is known about such features of ^{99m}Tc-MIBI SPECT in pituitary adenomas.

The present study evaluated whether ^{99m}Tc-MIBI SPECT might correlate with cavernous sinus invasion, proliferative potential, or Pgp expression, as encoded by the multidrug resistance gene-1 (*MDR-1*) messenger ribonucleic acid (mRNA), in pituitary adenomas (24, 25).

MATERIALS AND METHODS

We studied 15 patients with pituitary adenoma who were surgically treated in our hospital between April 1998 and December 2001. ^{99m}Tc-MIBI SPECT were performed preoperatively on 15 patients (five men, 10 women, age range from 25 to 68 yrs, mean age 47.7 yrs). For this study, an explanation of its objects and methodology was performed to all patients and their families. The tumor samples were classified by histological subtype according to hormone production; they included 10 nonfunctioning adenomas, 2 prolactinomas, 2 GH producing adenomas, one ACTH producing adenoma. A portion of each tumor was sanap-frozen immediately after resection by immersion into nitrogen and fixed in formalin fixative for paraffin embedding.

Cavernous sinus invasion by tumor was defined on the basis of MRI findings, and was determined as invasion in whose grade is higher than 2 of the classification by Knosp *et al* (15).

^{99m}*Tc-MIBI SPECT Imaging*

Isotope imaging was performed with a fan-beam collimater and a triple head gamma camera (Picker Prism 3000; Picker International, Cleaveland, OH). This camera was interfaced with a dedicated computer (ODYSSEY; Picker International). Patients were given doses of 600 MBq ^{99m}Tc-MIBI injected intraveneously. Early SPECT acquisition was performed 15 minutes after the injection of each radioisotope, whereas delayed SPECT images were acquired 3 hours after injection. Three energy analyzers were used for acquisition, and these were set at 140-KeV with 15% window for ^{99m}Tc images. These projection data were processed with a two-dimensional low-pass filter, then corrected for contamination scatter. Transverse, coronal, and sagittal sections were reconstructed. The system was 7.2 mm full width at half maximum, and the slice thickness was 6.88 mm. In order to eliminate such contamination scatter, the raw ^{99m}Tc data were corrected according to the equations in each pixel. SPECT images were compared with brain magnetic resonance (MR) images, and accumulation in pituitary adenomas was evaluated by the same radiologist. Semiquantitative analysis of abnormal uptake of the two radiopharmaceuticals was performed by drawing identical regions of interest (ROIs) over the tumor uptake area and the normal brain on one transverse section that demonstrated the lesion most clearly, which region was carefully selected on both early and delayed images. The mean ROI values (total counts/ total pixels) were measured, and the tumor-to-normal brain (T/N) ratios were obtained. The T/N ratio of the early images was called the early ratio (ER), and the T/N ratio of delayed image was called the delayed ratio (DR). For semiquantitative evaluation of the degree of retention in the lesion, the retention index (RI) was calculated using the following formula: (DR-ER)/ER×100%.

Immunnohistochemistry

Pgp expression was evaluated immunohistochemically on formalin-fixed, paraffin-embedded sections using monoclonal antibodies (MAbs) against Pgp (JSB-1, Progen Biotechnik, Heiderberg, Germany). Proliferative potentials were examined using MIB-1 MAb (Immunotech, Marseille, France) against Ki-67 antigen by means of the streptavidin-biotin method.

Six-micron sections were deparaffinized in xylene, rehydrated through graded alcohols, and immersed for 15 minutes in phosphate-buffered saline (PBS). For antigen retrieval, the sections were microwaved in a 0.01 M citrate buffer (pH 6.0) for 20 minutes. After microwave pretreatment, the endogenous peroxidase activity was blocked by immersion in a 3% hydrogen peroxidase/methanol solution for 10 minutes, and nonspecific staining was then blocked by a 20-minute incubation with normal horse serum. The sections were then incubated overnight at 4°C with primary antibodies (JSB-1, 1 : 50 dilution ; MIB-1, 1 : 50 dilution) in a humidity chamber. The sections were treated for 30 minutes. with biotinylated horse secondary antibody against mouse immunoglobulins (ABC Elite, Vector Lab., Burlingame, Calfornia, U. S. A.) and for 30 minutes. with avidin-biotin complex (ABC Elite), followed by 0.06% diaminobenzidine with 0.01% hydrogen peroxidase for 5 minutes. The slides were lightly counterstained with hematoxylin. Control groups were obtained by omitting the primary antibody. The tumors were classified into two groups according to the degree of Pgp immunostaining as follows: Tumors that had no staining or less than 5% of specimens were referred to as "-" ; those with diffuse positivity and dense or moderate staining were referred to as "+"

The MIB-1 LI was calculated as the percentage of tumor cells that tested MIB-1 positive. More than 500 tumor cells in randomly chosen microscopic fields were examined, and the percentage of MIB-1 positive cells was calculated.

Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was isolated from the frozen tissue sample using ISOGEN reagent (Nippon Gene, Toyama, Japan). In brief, 100mg of each tissue was homogenized in 1ml of ISOGEN. Subsequently, 0.2 ml of chloroform was added and the mix was centrifuged. This separated the solution into an aqueous phase containing RNA, an interphase containing DNA, and an organic phase containing protein. The aqueous layer was aspirated and added to 0.5 ml of isopropanol for RNA precipitation. Following this, the solution was centrifuged, then the pellet was washed with 75% ethanol and centrifuged. Afterward, RNA was collected into 50 μl of diethylpyrocarbonate (DEPC)-treated water. RT-PCR was performed using a First-Strand cDNA Synthesis Kit (Amarsham Pharmacia Biotech, Woerden, The Netherlands). One microliter of total RNA (1μg) was added to 14 l of RT-mixture. After mixing, the samples were incubated at 37°C for 45 minutes, 95°C for 5 minutes, and 4°C for at least 5 minutes. We synthesized two oligodeoxynucleotide primers with the sequences 5'-GCCTGGCAGCTGGAAGACAA ATACACAAATT-3' and 5'- CAGACAGCAGCTGACA GTCCAACAACAGGACT-3' for *MDR-1* (16), and 5'- A TCACCATTGGCAATGAGCG -3' and 5'-TTGAAGG TAGAAACGTGGAT-3' for β actin. Thirty five microliters of a PCR-mixture containing 10nM primers and Taq DNA polymerase (Amershan Pharmacia Biotech) was added to the RT-products. Initial denaturation for 2 minutes at 94°C was followed by 30 cycles of 1 minute at 94°C, 1 minutes at 55°C, 2 minutes at 72°C, and a final extension for 6 minutes at 72°C. The PCR-products were separated on 2% agarose gels, and ethidium bromide-stained bands were recorded by Mupid-2 R (Cosmo-Bio, Tokyo, Japan). The expressed sizes of the PCR products were 283 bp for *MDR-1* and 93 bp for β actin.

Statistical analysis

Correlations among the factors were evaluated using Pearson correlation coefficient (r). The values of the each T/N ratio and RI were expressed as the mean ± standard error. To test for differences between these parameters, the Student's t-test was used. Correlation was analyzed using the Pearson Product moment test and linear regression. Results were considered significant at the level of $p<0.05$.

RESULTS

Among the 15 cases with pituitary adenomas, all were macroadenomas (more than 10mm diameter), and five cases showed cavernous sinus invasion. The clinical, ^{99m}Tc-MIBI SPECT, and immunohistochemical data are summarized in Table 1.

All cases showed positive uptake on both ER and DR for ^{99m}Tc-MIBI SPECT (Fig. 1). No correlation was found on the ER, DR, RI of the ^{99m}Tc-MIBI SPECT among the functional type of pituitary adenomas.

The results of Pgp immunohistochemistry are also summarized in Table 1. Positive reactions for Pgp were detected, mainly in the cytoplasm of tumor cells, in 6 of 15 (40%) pituitary adenomas (Fig. 2).

In five cases out of 15 pituitary adenomas, the expression of *MDR-1* mRNA was investigated by RT-PCR assay. RT-PCR products were visualized

Table 1. Clinical, single photon emission computed tomography(SPECT), imunohistochemical, and molecular biological characteristics of 15 patients

Case No.	Age (yr)	Sex	Size (mm)	Cavernous invasion	^{99m}Tc-MIBI-SPECT ER	DR	RI(%)	Pgp	*MDR-1* mRNA	MIB-1 LI (%)	Function
1	52	F	13×15	−	42.65	28.48	−33.2	+	+	2.6	GH
2	65	M	35×32	−	143.70	99.22	−31.0	+	−	2.2	NF
3	42	F	23×24	−	13.93	7.75	−44.4	+	+	0.9	NF
4	46	M	10×11	−	13.00	10.00	−23.1	+	n.d.	0.1	GH
5	30	F	12×10	−	51.55	11.55	−77.6	+	n.d.	0.1	PRL
6	25	F	10×10	−	19.22	15.00	−22.0	+	n.d.	0.0	NF
7	42	M	30×28	−	15.46	18.00	16.4	−	−	2.5	NF
8	68	M	25×20	−	47.53	42.79	−10.0	−	n.d.	2.1	NF
9	53	M	21×19	−	57.79	55.83	−3.4	−	−	1.3	NF
10	25	F	10×10	−	20.75	17.57	−15.3	−	n.d.	1.0	NF
11	36	F	10×12	+	36.38	37.75	3.8	−	n.d.	0.1	ACTH
12	64	F	24×20	+	17.13	13.11	−23.5	−	n.d.	1.5	NF
13	52	F	25×25	+	115.81	71.55	−38.2	−	n.d.	0.5	NF
14	66	F	20×18	+	8.52	5.80	−31.9	−	n.d.	0.1	NF
15	50	F	25×22	+	185.83	111.75	−39.9	−	n.d.	0.8	PRL

ER : early ratio, DR : delayed ratio, RI : retention index, LI : labeling index, n.d. : not done,
NF : nonfunctioning adenoma, PRL : prolactin producing adenoma, GH : growth hormone producing adenoma,
ACTH : adorenocorticotropic hormone producing adenoma, Pgp : P-glycoprotein,
^{99m}Tc-MIBI-SPECT : technetium-99m-methoxyisobutylisonitrile single photon emission computed tomography

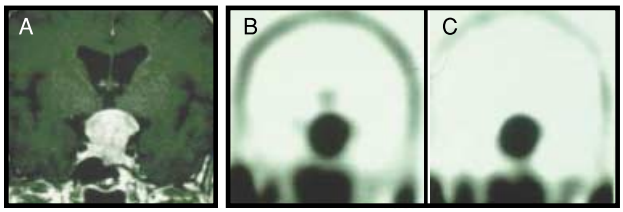

Fig. 1 : Neuroimaging findings in a 42-year-old male with nonfunctioning pituitary adenoma. Postcontrast T1-weighted corenal magnetic resonance image (A) shows a tumor in the pituitary region. Both early (B) and delayed (C) images of technetium-99m sestamibi single photon emission computed tomography show an intense accumulation corresponding to the lesion.

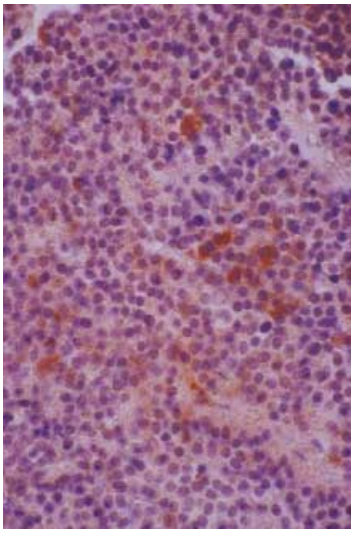

Fig. 2 : Photomicrograph showing positive immunohistochemical reactivity for P-glycoprotein, diffusely in the cytoplasm and nulceus of tumor cells. Original magnification × 200

with ethidium bromide, which clearly showed the band of interest (293 bp) (Fig. 3). The expression of *MDR-1* mRNA was clearly seen in 2 of 5 (40%) specimens by RT-PCR assay. Two cases with *MDR-1* mRNA overexpression and one of three cases with no *MDR-1* mRNA expression showed positive Pgp immunoreactivity, whereas other two cases with no *MDR-1* expression were negative for Pgp. This result indicated that Pgp levels were increased according to the expression of *MDR-1* mRNA, and that Pgp may be regulated through *MDR-1* mRNA expression.

Neither ER, DR, nor RI on ^{99m}Tc-MIBI SPECT correlated with MIB-1 LI.

The RI (-38.55±20.77%) on ^{99m}Tc-MIBI SPECT of cases with Pgp positive expression was significantly lower than that (-15.78±19.40%) of cases without Pgp expression (p=0.0494) (Table 2). The ER or DR on ^{99m}Tc-MIBI SPECT did not correlate with Pgp expression (Table 2).

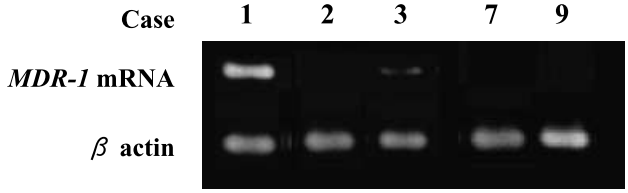

Fig. 3 : Ethidium bromide-stained agarose gel showing reverse transcription-polymerase chain reaction analysis of multidrug resistance gene-1 (*MDR-1*) mRNA expression (293 bp) in pituitary adenomas (upper line). Two of five cases showing overexpression of *MDR-1* mRNA. The lower line represents β actin, which was used as a control.

Table 3. Comparison of 99 mTc-MIBI findings in the Pgp positive and negative groups

	^{99m}Tc-MIBI -SPECT		
	ER	DR	RI (%)
Pgp positive group (n=6)	47.34±49.82	27.50±32.55	-38.55±20.77*
Pgp negative group (n=9)	56.13±58.68	41.57±34.00	-15.78±19.40*

Values are mean±standard deviation. ER : early uptake ratio, DR : delayed uptake ratio, RI : retention index
Pgp : P-glycoprotein,
^{99m}Tc-MIBI-SPECT : technetium-99 m-methoxyisobutylisonitrile single photon emission computed tomography
*Significance difference between Pgp positive and negative groups (Student's t-test, $p<0.05$)

DISCUSSION

^{201}Tl-Cl -SPECT, which is useful for diagnosing a variety of tumors, and also for evaluating the degree of malignancy or proliferative potential in brain tumors (4, 5, 17-21), is available for detecting biological aggressiveness such as cavernous invasion or proliferative potential in pituitary adenomas, to determine the indication for surgical treatment (6). On the other hand, ^{99m}Tc-MIBI SPECT are also useful to evaluate the histological grade or proliferative potential in gliomas (7, 8, 22, 23). However, there are few reports regarding the relationship between ^{99m}Tc-MIBI SPECT findings and proliferative potential or cavernous invasion in pituitary adenomas (24, 25). Our study revealed that ^{99m}Tc-MIBI SPECT findings do not correlate with either MIB-1 LI or cavernous sinus invasion in pituitary adenomas.

^{99m}Tc-MIBI uptake is reported to distribute to normal structures of choroid plexus and the pituitary gland (9). Kojima *et al*. (24)suggested that ^{99m}Tc-MIBI was not taken up in the normal pituitary gland but in the dorsum sellae or clivus, whereas they evaluated the uptake of ^{99m}Tc-MIBI in microadenomas.

The mechanism for ^{99m}Tc-MIBI uptake and washout in pituitary adenomas is not clear. The uptake of ^{99m}Tc-MIBI depends on the distribution of regional blood flow and on mitochondrial oxidation capacity, which is an indicator of cell viability (17, 26, 27). In addition, ^{99m}Tc-MIBI SPECT is known as capability of predicting patient's response to chemotherapy in cases of malignant tumors because decreased accumulation of ^{99m}Tc-MIBI implies the presence of Pgp, which also transports chemotherapeutic agents outward from the tumor cell (9, 28-32). In gliomas, Andrews *et al*.(33) found the correlation between ^{99m}Tc-MIBI SPECT findings and *MDR-1* gene expression in 6 glioma cases, and they supported the use of ^{99m}Tc-MIBI SPECT as a non-invasive method for detecting *MDR-1* gene expression in gliomas. On the other hands, Shibata *et al*.(34) reported that Pgp expression of both tumor cells and vascular endothelial cells showed no correlation with ^{99m}Tc-MIBI SPECT findings in 26 gliomas. To date, however, little has been known about the relationship between the expression of Pgp and ^{99m}Tc-MIBI SPECT findings in pituitary adenomas (24, 25). Pgp or MRP expression in pituitary adenomas has not been reported in the literature. Our study revealed that Pgp was expressed in 6 of 15 (40%) pituitary adenomas, and two of 5 (40%) cases showed *MDR-1* mRNA overexpression by RT-PCR assay. There seems to be correlation between these two data. Our study also revealed that the RI on ^{99m}Tc-MIBI SPECT correlated significantly with Pgp expression. These results indicate that Pgp, an *MDR-1* gene product, contributes as a washout mechanism of ^{99m}Tc-MIBI in pituitary adenomas.

In this study, the washout rate was defined as the difference in uptake ratio between 15 min. and 3 hrs after injection of ^{99m}Tc-MIBI. It is not known whether the Pgp-mediated transport of radioactivity is a rapidly functioning mechanism or not, such that Pgp transport is already completed within 15 min after injection of ^{99m}Tc-MIBI. It has recently been reported that ^{99m}Tc-MIBI is a substarte not only for Pgp but also for multidrug resistance associated protein (MRP)(11). The retention of ^{99m}Tc-MIBI in cells might depend on both Pgp and MRP expression, therefore further studies with simultaneous measurement of MRP expression in pituitary adenomas are also necessary. Neither *MDR-1* (Pgp) nor MRP expression in pituitary adenomas have been reported in the literature.

Though pituitary adenomas are generally a clinically benign tumor, some of tumor recur and develop invasion. It is therefore important to predict aggressive behavior. Although the number of patients in the present study was small, we believe that ^{99m}Tc-MIBI SPECT may not be available in determining the proliferative potential or invasion. Then, the washout mechanism of ^{99m}Tc-MIBI may be associated with the Pgp expression in pituitary adenomas.

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