Evaluation of Fluorine-18-BPA-Fructose for Boron Neutron Capture Treatment Planning


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Boron neutron capture therapy (BNCT) using 4-[\(^{10}\)B]boronophenylalanine-fructose (BPA-Fr) is in Phase II clinical trials to validate BNCT as a treatment for glioblastoma multiforme and melanoma. Successful BNCT depends on knowledge of the distribution of boron-containing agents in both tumor and normal tissue as currently determined by chemical confirmation of boron deposition in surgically removed malignant tissue before BNCT. **Methods:** We used PET to noninvasively obtain in vivo information on the pharmacokinetics of the \(^{18}\)F-labeled analog of BPA-Fr in two patients with glioblastoma multiforme. Time-activity curves generated from the bolus injection of \(^{18}\)F-BPA-Fr were convolved to simulate a continuous infusion used for BNCT therapy. **Results:** Distribution of \(^{18}\)F-BPA-Fr by PET was found to be consistent with tumor as identified by MR imaging. The \(^{18}\)F-BPA-Fr tumor-to-normal brain uptake ratio was 1.9 in Patient 1 and 3.1 in Patient 2 at 52 min after injection. The \(^{18}\)F-BPA-Fr uptake ratio in glioblastoma paralleled that of nonlabeled BPA-Fr seen in patients as previously determined by boron analysis of human glioblastoma tissue obtained from pre-BNCT surgical biopsy. **Conclusion:** Knowledge of the biodistribution of BPA-Fr enables pre-BNCT calculation of expected tissue dosimetry for a selected dose of BPA-Fr at a specific neutron exposure. Fluorine-18-BPA-Fr PET is capable of providing in vivo BPA-Fr biodistribution data that may prove valuable for patient selection and pre-BNCT treatment planning.

**Key Words:** fluorine-18-BPA-fructose; positron emission tomography; boron neutron capture therapy

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Boron neutron capture therapy (BNCT) is based on the delivery of \(^{10}\)B to tumor cells followed by exposure of those cells to a neutron source. Absorption of a thermal neutron by a \(^{10}\)B atom produces lithium ions and alpha particles by nuclear disintegration. Interaction of the alpha particle with the tissue results in cell destruction within 10 \(\mu\)s of the original boron atom. Successful BNCT therapy is dependent on delivery of an adequate quantity of \(^{10}\)B to the tumor cells (1-3). Early clinical BNCT trials failed, in part, because the relative in vivo boron distribution could not be determined before the therapy (4). In recent years, significant advances have been made in the development of tumor-selective, boron-containing agents and clinical trials have resumed (5). Currently, BNCT treatment planning is hampered by the necessity of estimating boron distribution by analysis of tumor tissue removed by pre-BNCT debulking surgery. To address this issue, we developed boron-MRI methods for determining the in vivo distribution of BNCT agents (6,7). These MRI methods have met with limited success because they are dependent on \(^{11}\)B rather than \(^{10}\)B and thus require a double administration of the BNCT agent (once for MRI and once for BNCT). Boron-10 possesses extremely poor magnetic resonance characteristics and is not amenable to MRI using current clinical MRI units (8). Nevertheless, \(^{11}\)B MRI has been used to evaluate the distribution of a BNCT agent in a human (9).

An alternative approach to determine the kinetics of BNCT agents is using radiolabeled analogs of the boronated BNCT agents with PET. We have used amino acids labeled with positron-emitting radionuclides to evaluate tumors using PET (10-13). This report describes a method for using PET imaging to evaluate the biodistribution and pharmacokinetics of 4-\(^{11}\)B]boron-2-[\(^{18}\)F]fluoro-L-phenylalanine-fructose (\(^{18}\)F-BPA-Fr), an analog of the boronated phenylalanine currently being evaluated in BNCT Phase I/II clinical trials, in two patients with glioblastoma multiforme.

**MATERIALS AND METHODS**

Two patients with clinical and MRI suspicion of glioblastoma multiforme were referred for \(^{18}\)F-BPA-Fr PET. The patients in this study gave informed consent for the procedure, which was performed according to the guidelines of the UTMCK Radiation Safety Committee, Radioactive Drug Research Committee and the UTMCK Institutional Review Board.

Fluorine-18-BPA-Fr was prepared using the method previously described with minor modifications (14,15); \(^{18}\)F was produced through the \(^{18}\)O(p,n) \(^{19}\)F reaction using an RDS 112 cyclotron (CTI, Knoxville, TN). The target gas was then passed through 300 mg of freshly fused sodium acetate and the resultant \(^{18}\)FACoOF bubbled into a 25-ml conical reaction vessel containing 100 \(\mu\)mol \(^{18}\)BPA-HCl (Boron Biologicals, Inc., Raleigh, NC) in 5 ml of trifluoroacetic acid. The solution was stirred for 5 min at room temperature and then the trifluoroacetic acid was removed under reduced pressure. Acetic acid (0.1%, 3 x 0.5 ml) was used to dissolve the residue that was then filtered through a 0.22-\(\mu\) filter membrane (Millipore Corp., Bedford, MA) and loaded on to a VICI remote injector. The \(^{18}\)F-BPA was purified by reverse-phase HPLC separation using a Radial Compression Module (RCM, Waters Corp., Milford, MA) containing a Delta-Pak C18 guard column and column (25 mm i.d. x 10 mm length and 25 mm x 100 mm, respectively) and a PIN diode radioactivity detector (Bioscan, Inc., Washington, DC). Acetic acid (0.1%) was used as the mobile phase with a flow rate of 9.9 ml/min. The \(^{18}\)F-BPA eluted between 28 and 32 min; this fraction was reduced in volume under vacuum and filtered through a 0.22-\(\mu\) sterile filter (Millipore Corp.) into a sterile vial containing aqueous fructose (1.0 ml, 0.5 M) and sodium bicarbonate (0.5 ml, 8.4%). The radiochemical yield of \(^{18}\)F-BPA-Fr averaged 25% (53 mCi, 2.0 GBq) corrected to EOB and based on \(^{18}\)F-AcO. The synthesis time was 88 min. Quality control was performed on the final product for radiochemical identity and purity, radionuclidic purity, sterility, pH and pyrogenicity before injection.

PET images were obtained using an ECAT EXACT 921 whole-body PET system (Siemens/CTI, Knoxville, TN) that produces 47 image slices over a 16.2-cm axial field of view. The spatial resolution of the system is 6.5 mm in the x-y plane and 7.
mm along the z-axis. Transmission scans were obtained before tracer administration for attenuation correction. PET scan data acquisition was initiated simultaneously with intravenous administration of 370 MBq (10 mCi) of \(^{18}\text{F}\)-BPA-Fr injected over 30 sec. Dynamic emission images were acquired using twelve 10-sec frames, five 60-sec frames and six 5-min frames, followed by 10-min frames up to 2 hr postinjection, as tolerated by the patient. All images were reconstructed using measured attenuation correction with filtered backprojection, a zoom factor of 2 and a 0.35 pixel Hann filter.

Time-activity curves (TACs) were plotted for tumor and reference ROIs in contralateral normal brain and skull. The arterial blood concentration input function for tracer kinetic analysis was obtained from a ROI representing vascular activity in the internal carotid artery seen on the early bolus images applied to the remaining dynamic images. The vascular time-activity curve was fitted to a linear rise to peak activity followed by a double exponential washout using MATLAB (Mathworks, Inc., Natick, MA) data analysis software. Correction for partial volume effects on the blood curve was performed using a method previously described by Smith (16). This method has been shown to give recovery coefficient values equivalent to the Hoffman method (17) when using ROIs of the same size as the object size. Tissue-to-blood spillover was assumed to be negligible in the late time frames of the study.

Tumor ROIs were drawn on each image plane in which tumor was visible on the final time frame. ROI activity values were calculated by applying those ROIs to all time frames and calculating a weighted average based on the volume of tumor in each plane. Cortal brain ROIs were drawn in the contralateral normal brain on the final time frame and applied to all images in the dynamic sequence.

The compartmental model shown in Figure 1 was used to describe the kinetics of \(^{18}\text{F}\)-BPA-Fr in glioblastoma. The model consists of a vascular space, \(C^v\) (MBq/ml), and a tissue space, \(C^t\) (MBq/ml). Each of these spaces has a defined diffusible component, \(C_D\), and a nondiffusible component, \(C_{ND}\). This model represents an extension of the three-compartment model previously described by Imahori (18) for determining the incorporation rate of \(^{18}\text{F}\)-BPA in glioblastoma. The rate constants \(K_1\) to \(K_3\) are the same for the three-compartment model described by Huang (19) for \(^{18}\text{F}\)-2-fluoro-2-deoxyglucose. The current model differs from the three-compartment model by a compartment, \(C_{ND}^c\), that represents protein and RBC binding of \(^{18}\text{F}\)-BPA-Fr in whole blood as well as the appearance of possible \(^{18}\text{F}\)-BPA-Fr metabolites in whole blood. The parameter \(K_5\) represents an averaged transfer constant for retention of \(^{18}\text{F}\)-BPA-Fr in whole blood as well as appearance of metabolites in the vascular space from outside the ROI (20). In this analysis, \(K_5\) was assumed to be zero.

Differential equations for the model can be written:

\[
\begin{align*}
\dot{X}(t) &= AX(t) + BU(t) \\
Y(t) &= CX(t) + DU(t)
\end{align*}
\]

where \(X(t)\) is a column vector \([C_D^v(t), C_D^t(t), C_{ND}^v(t)]\); \(U(t)\) is the arterial input activity, \(C_D(t) = C_D^v(t) + C_{ND}^v(t)\) (MBq/ml), measured from a carotid artery blood-pool time-activity curve after intravenous injection of \(^{18}\text{F}\)-BPA-Fr; and \(Y(t)\) is the measured tissue activity. Both \(C_D(t)\) and \(Y(t)\) are determined using PET ROI analysis. Matrix \(A\) is given by:

\[
\begin{bmatrix}
- (K_3 + K_4) & 0 & 0 \\
- K_1 & - (K_2 + K_3) & K_4 \\
0 & K_3 & - K_4
\end{bmatrix}, \quad \text{Eq. 2}
\]

where the kinetic transport constants are defined as in Figure 1. \(B\) is a column vector \([K_5; K_1; 0]\); \(C\) is a row vector \([0; 1; 1]\); \(D\) is a scalar \([V]\) and \(t\) is a time variable (min). \(V\) is the estimated vascular fraction. Estimates of the parameters \(K_1\) to \(K_5\) and \(V\) were determined using a Levenberg-Marquardt analysis package (Ctrlc, Systems Control Technology, Palo Alto, CA).

Once the rate constants are determined from the bolus \(^{18}\text{F}\)-BPA-Fr data, a simulation analysis can be performed using an assumed constant infusion response curve, \(U(t)\), for BPA-Fr. Solving Equation 1 for \(Y(t)\) where the parameter matrices \(A, B, C\) and \(D\) are now known then gives a theoretical response curve to a continuous infusion of BPA-Fr as used in BNCT.

**RESULTS**

**Patient 1**

The first patient was a 62-yr-old woman who presented with encephalopathy. Differential diagnostic considerations included stroke, tumor and subdural hematoma. An enhanced MRI study showed multifocal structural abnormalities in the left parietal region suggesting a glioblastoma. A 52-min dynamic \(^{18}\text{F}\)-BPA-Fr PET scan was performed 1 wk before craniotomy. Biopsies were consistent with glioblastoma multiforme. Given the location of the tumor in the dominant hemisphere, it was felt that extensive resection was not indicated. The PET study (Fig. 2) showed areas of intense focal uptake of \(^{18}\text{F}\)-BPA-Fr in the left parietal and occipital lobes. Distribution of the \(^{18}\text{F}\)-BPA-Fr was localized to the tumor region previously identified on the MRI images, as well as activity remaining in the sagittal sinus and the skull. Time-activity curve analysis (not shown) of the tumor and contralateral normal brain tissue demonstrated increasing uptake of tracer in the tumor throughout the study period after an initial transit of activity in the vascular space. At the end of the 52-min uptake period, the tumor-to-normal brain tissue ratio peaked at 1.9:1. Peak tumor to skull activity was 2.2:1.

**Patient 2**

The second patient was a 64-yr-old woman with a 3–4 wk history of headaches, visual disturbances and difficulty with coordination of her left arm. A CT scan demonstrated a large right parietal mass consistent with a glioma. The patient had a 130-min dynamic \(^{18}\text{F}\)-BPA-Fr PET scan 1 day before craniotomy. Immunohistochemistry established the diagnosis of glio-
blastoma multiforme, Grade 3/4. The bulk of the tumor was solid, and there was minimal evidence of necrosis.

The $^{18}$F-BPA-Fr PET study (Fig. 3) showed an area of intense uptake in the right posterior parietal region corresponding to the location of the lesion seen on CT. PET time-activity curve analysis demonstrated a peak tumor-to-contralateral normal brain activity ratio of 3.4:1 8 min after injection of $^{18}$F-BPA-Fr (Fig. 4) with a subsequent decline to 2.6:1 at 120 min. Tumor-to-skull concentration was 2.1:1 at 8 min after injection but rose to a peak of 3.3:1 at 120 min after injection. At 52 min postinjection, the ratios of tumor-to-brain and tumor-to-skull were each 3.1:1, while the tumor-to-blood activity ratio was 2.1:1. A second $^{18}$F-BPA-Fr scan done 6 wk postcraniotomy showed residual focal uptake in the medial portion of the original tumor, corresponding to a site of known remaining tumor as confirmed by the neurosurgeon (Fig. 5).

Time-activity curve analysis of the residual tumor yielded results similar to those obtained before surgery.

**Model Analysis**

The kinetic rate constants for the compartment model shown in Figure 1 were determined using a Levenburg-Marquardt algorithm for tumor and brain tissue. Table 1 shows the calculated rate constants for two tumors seen in Patient 1 (Studies 1A and 1B), a single tumor before and after surgery on Patient 2 (Studies 2 and 3) and corresponding contralateral cortical brain tissue. The average model rate constants for tumor were estimated to be as follows ($k_i$ fixed at 0.0): $k_1=0.053$ min$^{-1}$, $k_2=0.927$ min$^{-1}$, $k_3=0.075$ min$^{-1}$, $k_4=0.002$ min$^{-1}$ and $k_5=0.032$ min$^{-1}$. The vascular fraction, $V$, was estimated to be 0.01 ml/g. The calculated curve fit for Patient 2, Scan 1, is shown in Figure 3 (solid line). For normal brain tissue, the average parameter values were estimated to be ($k_i$ fixed at 0.0): $k_1=0.014$ min$^{-1}$, $k_2=0.392$ min$^{-1}$, $k_3=0.029$ min$^{-1}$, $k_4=0.002$ min$^{-1}$ and $k_5=0.013$ min$^{-1}$. The vascular fraction for normal brain was 0.01 ml/g. The net forward flux, calculated by the macroparameter, $K = k_k/(k_2+k_3)$ averaged 0.0041 for tumor and 0.0010 for normal brain.

Figure 6 contains the results of the simulation analysis using the data generated from the image in Figure 4, assuming a 30-min continuous infusion of $^{18}$F-BPA-Fr as is done for clinical BNCT. As expected, the maximum tumor-to-blood activity ratio is the same as with a bolus infusion. The tumor-to-brain ratio is greater than 3.0 until 72 min after initiation of a 30-min infusion. At this time, there is predicted maximal uptake of BPA-Fr in the tumor. The maximum global tumor-to-brain $^{18}$F-BPA-Fr uptake ratios were greater than 2.1:1 for each of the other two patients.

**DISCUSSION**

Published reports suggest that success of BNCT depends on the tumor selectivity of the boronated agent to be high enough to ensure a tumor-to-normal tissue boron content of greater than 3:1 (2). Currently, the boron contents of the targeted and surrounding tissues are determined by chemical measurements of tissue samples harvested during tumor debulking surgery. Tissue samples are analyzed by direct current plasma atomic emission spectroscopy (DCP-AES) (21,22), and the results are used to decide whether patients are likely to benefit from BNCT. Clearly, a noninvasive method for determining boron distribution to appropriately identify patients for BNCT would be valuable, especially in patients who are poor surgical candidates and are considered for BNCT. Boron-MRI is currently restricted to the detection of $^{11}$B and, thus, has been used only sparingly (8,9). Ishiwata (23,24) successfully labeled BPA with $^{18}$F-BPA for preliminary evaluation of this agent in tumors. For the study presented in this report, a synthesis was developed to make a fructose complex of $^{18}$F-BPA, $^{18}$F-BPA-Fr, a fluorinated analog of the agent currently being used in BNCT clinical trials at Brookhaven National Laboratory (13).

To evaluate the potential of PET to assist in BNCT treatment planning, $^{18}$F-BPA-Fr was administered to two GBM patients who were then examined using PET. In Patient 2 the tumor-to-normal brain concentration ratio of $^{18}$F-BPA-Fr was 3.1:1 at 52 min after injection. Figure 6 contains the results of a simulation analysis using the data generated from the image in Figure 4 to estimate the kinetics of BPA-Fr, assuming a 30-min continuous infusion of BPA-Fr. As expected, the peak tumor-to-brain and tumor-to-marrow ratio occurs at a later time due to the duration of the infusion. A tumor-to-brain ratio greater than 3.0 is present until 72 min after initiation of a 30-min infusion. This
time also corresponds to the predicted maximal uptake of F-BPA in the tumor. In addition, the tumor-to-blood activity ratio appears to plateau after 60 min, suggesting that this is the optimal time for neutron exposure after infusion of BPA-Fr.

We used a four-compartment model for evaluation of the 18F-BPA-Fr tracer kinetics instead of the three-compartment model used by Imahori. This model has been used to evaluate cerebral blood flow and tracer retention kinetics of 99mTc-HMPAO (23,26). The model can be considered to be similar to the three-compartment model introduced by Huang for 18F-FDG and Imahori for 18F-BPA with an additional blood-pool compartment that corrects for the measurement of whole-blood activity detected by PET as opposed to arterial blood sampling. If plasma sampling with red blood cell and metabolite correction is performed, it may be possible to reduce the model to three compartments.

The kinetic rate constants varied between Patients 1 and 2, possibly due to differences in individual tumor uptake mechanisms. Nevertheless, the net incorporation rate of 18F-BPA-Fr, given by the parameter $k_1 k_2/(k_2 + k_3)$, was relatively constant for the tumors and averaged approximately four times that of the normal brain. The low value of $k_1 k_2/(k_2 + k_3)$ in tumor for Patient 2 after surgery (Study 3 in Table 1) could be due to postsurgical effects but more likely represents an artifact due to volume averaging and partial volume effects for the small residual tumor seen in the images.

The simulation analysis shown in Figure 6 can be performed using spreadsheet software by summing multiple bolus input functions evenly distributed during a simulated infusion period. This approach is independent of the model but only gives the total tissue activity for a given infusion period as a function of time. An advantage of the model approach is the determination of the concentrations of tracer in each compartment that may allow detailed modeling of the tracer concentration within cells or in the extracellular space for more accurate assessment of tissue dosimetry (27,28). Using Equation 1 with known 18F-BPA-F rate constants from PET coupled with the molar concentration ratio of 18B/18F, estimates of individual compart-

![Figure 5. Postoperative 18F-BPA-Fr PET scan of Patient 2 shows residual tumor uptake in the right posterior parietal region surrounding the area of prior surgical resection.](image)

**TABLE 1**

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<th>Tumor</th>
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<th>$k_2$</th>
<th>$k_3$</th>
<th>$k_5$</th>
<th>$V$</th>
<th>$k_1 k_2/(k_2 + k_3)$</th>
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<td>0.0010</td>
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* $k_4 = 0.002$ and $k_5 = 0.0$ for all cases.

$ k_1 $ and $ V $ reflect values corrected for partial volume correction.
ment $^{10}$B concentration can be obtained. Calculation of tissue radiodosimetry can be accomplished using Monte Carlo probability of cell destruction resulting from neutron interaction with the estimated compartmental extracellular and intracellular concentrations of BPA-Fr (29,30).

The current study produced images that are reminiscent of our earlier neuro-oncology studies using $^{11}$C-labeled DL racemates of tryptophan and valine (10), and especially the unnatural amino acid, $^{11}$C-labeled aminocyclobutanecarboxylic acid (ACBC). The rate of uptake of $^{18}$F-BPA-Fr appears to be slower than that of tryptophan or valine. Interestingly, Mishima's studies using $^{18}$F-BPA (not complexed with fructose) yielded PET images more closely resembling earlier phenylalanine PET studies. The difference in uptake kinetics between $^{18}$F-BPA-Fr and other amino acids may be due to the fructose complex that results in kinetics more similar to FDG.

Calculating tumor dosimetry from the $^{18}$F-BPA-Fr PET compartmental model data assumes uniform distribution of tracer activity within each compartment and, thus, yields a global average intracellular and extracellular activity concentration within a defined image region. Microdosimetry calculations will require more detailed knowledge of the histology and relationships of the model compartments to the cell structure.

We recognize that accurate parameter identification requires correction for known sources of error in PET quantification including spillover and partial volume effects, PET/well counter calibration and attenuation correction. We corrected for attenuation and PET/well counter calibration using a PET transmission scan and calibration phantom. In this study, the input function was corrected for partial volume effects using an image derived recovery coefficient. Partial volume error in tumor ROIs was not considered to be significant due to the size of the lesions. However, partial volume effects may explain the low value for the macroparameter $k_1k_2/(k_2+k_3)$ in Patient 2 after debulking surgery, in which only a small focus of tumor tissue was identified on the PET images.

Finally, in this model, the tracer kinetics of $^{18}$F-BPA-Fr are assumed to be the same for both PET and BNCT treatment doses (2 mg $^{18}$F-BPA-Fr for PET versus 25 g BPA-Fr for BNCT). This has been shown to be true for $^{18}$F-BPA by Imahori (18). The $^{18}$F-BPA-Fr tumor-to-brain uptake ratio of 3:1:1 seen in the PET images is similar to that determined by $^{10}$B analysis of tumor and brain tissue in patients infused with BPA-Fr before debulking surgery, suggesting that the kinetics are similar for the PET and BNCT doses. However, performing a $^{18}$F-BPA-Fr PET study simultaneously in a patient injected with a BNCT BPA-Fr treatment dose may help validate this premise.

**CONCLUSION**

The results from our patients' $^{18}$F-BPA-Fr PET data suggest that the optimal window for effective BNCT is 60–90 min postinjection of BPA-Fr assuming a 30-min infusion duration. These results correlate well with the current Phase II Clinical Trial Protocol in which neutron irradiation is initiated approximately 45 min following a 2 hr intravenous infusion of BPA-Fr. PET can potentially be used to determine not only the distribution of brain tumor tissue that can be treated using BNCT but also may be used to predict the optimal time for neutron exposure with BNCT, and by using Monte Carlo analysis of the tissue distribution, may also enable estimation of the radiodosimetry to the tumor tissue.

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**REFERENCES**

Parathyroid Hyperplasia, Thymic Carcinoid and Pituitary Adenoma Detected with Technetium-99m-MIBI in MEN Type I

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We report a case of a 57-yr-old woman with history of multiple endocrine neoplasia type I (MEN I). A \(^{99m}\)Tc-sestamibi scan demonstrated a hyperplastic parathyroid gland, a large anterior mediastinal mass and a pituitary adenoma during a study done to evaluate recurrent hyperparathyroidism. The importance of this case is that much of the nonparathyroid pathology in patients with MEN I syndrome may be detected with this one study.

Key Words: multiple endocrine neoplasia type I; sestamibi; carcinoid; parathyroid adenoma; hyperparathyroidism

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Type I multiple endocrine neoplasia (MEN I) is a hereditary autosomal dominant syndrome consisting of pituitary, parathyroid and pancreatic islet cell neoplasms (1). The clinical expression of each of the three major components of MEN I within and among affected families is variable. Hyperparathyroidism is the most common endocrine abnormality in MEN I, and is biochemically present in 90% of patients at the time of diagnosis (2–5).

Symptoms of MEN I typically appear during the third to fifth decades, but screening laboratory tests for asymptomatic hypercalcemia may identify affected individuals at an earlier age (4,6). The spectrum of symptoms and signs of hyperparathyroidism in MEN I is similar to that observed in sporadic primary hyperparathyroidism. The common clinical manifestations include urolithiasis, peptic ulcer disease, emotional liability and bone pain. Multiple parathyroid gland hyperplasia is the characteristic finding in MEN I related hyperparathyroidism (5).

CASE REPORT

The case of a 57-yr-old woman with MEN I is presented. The patient’s brother has hyperparathyroidism and a gastrinoma, and