Clinical Oncology: Case Reports

Case Report

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Partial Response to Dual *BRAF* and *MEK* Inhibition in a Patient with *BRAF*-Mutant Pancreatic Acinar Cell Carcinoma Refractory to Chemotherapy: A Case Report and Review of the Literature

Adriana PC Barrichello[1*], Allan AL Pereira[1], Maria Dirlei FS Begnami[2], Marcus Vinicius Grigolon[3], Eduarda SC Oliveira[4], Gustavo S Fernandes[1]

Abstract

Introduction: Pancreatic Acinar Cell Carcinoma (PACC) is a rare subgroup of pancreatic neoplasms that has a better prognosis compared to Pancreatic Ductal Adenocarcinoma (PDAC). The more indolent evolution of the PACC makes surgical resection the standard treatment for localized disease. In metastatic disease, treatment is not well established. BRAF mutations have been detected in up to 13% of PACC, however, treatment with *BRAF* and/or *MEK* inhibitors has not yet been studied.

Case report: We present the case of a 73-year-old man, who has the diagnosis of *BRAF*-mutated metastatic PACC refractory to chemotherapy regimens. He underwent the combination of dabrafenib (selective *BRAF* inhibitor) and trametinib (selective *MEK* inhibitor) and had a partial response after 2 and 6 months from initiation of treatment.

Discussion: This case suggests the hypothesis that the block of the *RAS-RAF-MAPK* pathway with the combination of dabrafenib and trametinib may be an option in patients with *BRAF*-mutated refractory metastatic PACC. However, other studies are currently evaluating combinations of *BRAF* and *MEK* inhibitors in non-melanoma and non-colorectal cancer BRAF-mutated tumors, that can help confirm the activity of dual *MEK/BRAF* inhibition as a standard approach in *BRAF*-mutant PACCC

Keywords

Pancreatic acinar cell carcinoma; Pancreatic neoplasms; *BRAF* mutations; *BRAF* inhibitor; *MEK* inhibitor

Introduction

Pancreatic carcinomas with acinar differentiation are a very rare subgroup of pancreatic neoplasms, accounting for 1%-2% of malignant exocrine pancreatic tumors in adults [1]. This particular subgroup includes the following subtypes: Pancreatic Acinar Cell Carcinoma (PACC), pancreatoblastoma, and carcinomas of mixed differentiation, where PACC is the most common.

Pancreatic carcinomas with acinar differentiation are more prevalent in men (male-to-female ratio of 3.6:1) and most cases occur in adults with a mean age of 56 at diagnosis, although pancreatoblastomas usually affect children under 10 years old [2-4].

Patients with PACC have a better prognosis than those with Pancreatic Ductal Adenocarcinoma (PDAC) but a worse prognosis than those with pancreatic neuroendocrine tumors. Reports of overall survival range from 19 to 57 months [5].

Unfortunately, due to the scarcity of this subtype of pancreatic tumors, there is no randomized trial to guide optimal therapy sequencing. As in PDAC, the treatment of choice for PACC is surgical resection if the tumor is localized, with significant improvement in survival [3,6]. However, the impact of adjuvant chemotherapy or radiation on survival following surgical resection is difficult to determine in the absence of prospective data, and only limited conclusions can be drawn from retrospective series. For metastatic or unresectable tumors, due to the few cases that are present each year, most therapeutic regimens used are the same as those utilized for PDAC or colorectal carcinomas [5].

As in other tumors, the molecular profiling of PACC can be an option for patients with refractory disease. A review of PACC molecular profiling showed several gene alterations [7,8]; in particular, *BRAF* mutations were detected in 2% to 13% [8-10].

BRAF mutations are considered actionable in other solid tumors, such as colorectal cancer, melanoma and lung cancer. However, when treated with monotherapy with BRAF inhibitors, resistance rapidly appears. The vertical combination of *BRAF* and *MEK* inhibitors has demonstrated striking clinical efficacy; thus, it has become a standard of care in patients with *BRAF*-mutated melanoma and lung cancer [11-14] and has been studied for *BRAF*-mutated colorectal cancer [15,16].

Here, we report a case of a partial response to the combination of dabrafenib (selective *BRAF* inhibitor) and trametinib (selective *MEK* inhibitor) in a patient with *BRAF*-mutated metastatic PACC refractory to chemotherapy regimens.

Case Presentation

A 73-year-old Brazilian man presented with abdominal pain, with progressive worsening and weight loss. He had no significant past medical conditions or family history, and his physical examination was normal. The patient underwent a CT scan that demonstrated lymph node enlargement in the hepatic hilum, peripancreatic region, and interaortocaval chains as well as in the mesentery measuring up to 5.2 cm. There was also lymph node enlargement in the common iliac chains bilaterally, measuring up to 2.8 cm, and infiltration of the uncinate process and head of the pancreas by lymph node enlargement, leading to dilation of the main pancreatic duct.

A PET/CT scan showed an expansive pancreatic head lesion of 4.8 cm (SUV=8.1) and lymph node enlargement forming conglomerates

***Corresponding author:** Adriana PC Barrichello, Division of Medical Oncology, Hospital Sírio-Libanês, Brasília-DF, Brazil, E-mail: adriana.pcbarrichello@hsl.org.br

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in the portocaval, interaortocaval, mesenteric and bilateral common iliac space (SUV=9.1). Endoscopic ultrasound-guided biopsy revealed acinar cell carcinoma (Figures 1 and 2). Immunohistochemistry was positive for cytokeratin (AE1/AE3) and alpha 1 antitrypsin but negative for Synaptophysin (Sy) and Chromogranin A (CgA). Ki67 was found to be positive in 60% of cells.

The patient received neoadjuvant treatment with FOLFIRINOX for 5 months and then underwent duodenopancreatectomy.

The anatomicopathological study of the surgery confirmed acinar cell carcinoma, grade 3 (poorly differentiated) in the pancreatic head, grade 1 response to neoadjuvant chemotherapy, and the presence of perineural, lymphatic and hematologic carcinomatous invasion.

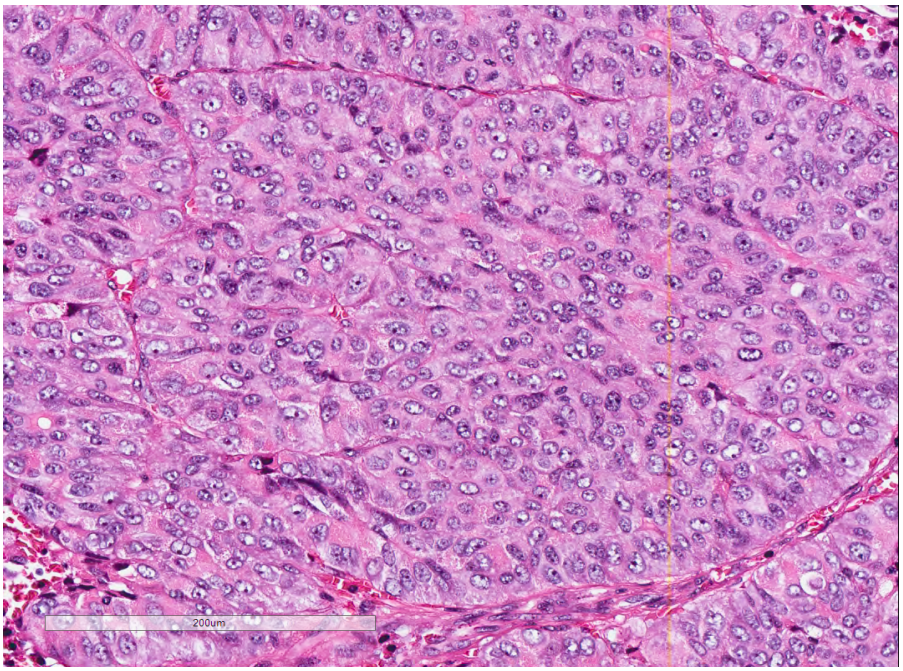

Figure 1: Acinar cell carcinoma showing a solid growth pattern, with sheets and nests of cells with proeminent, single nucleoli and amphophilic cytoplasm.

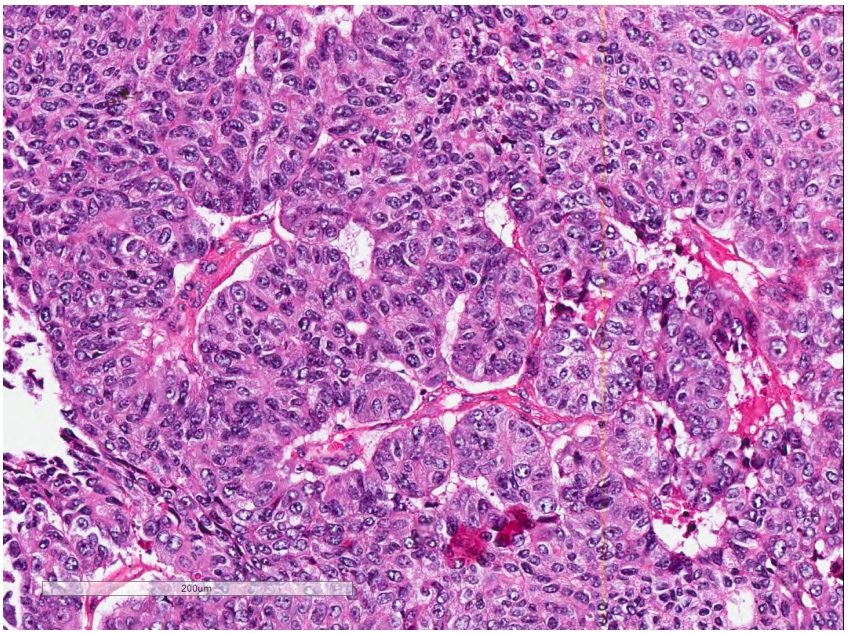

Figure 2: Area of acinar carcinoma showing acinar structures with pinpoint lumina and basally located nuclei.

The neoplasia infiltrated the peripancreatic adipose tissue (*ypT3*). Metastases were present in 11 of 21 peripancreatic lymph nodes, 4 of 13 periduodenal lymph nodes and 2 of 13 lymph nodes in the large gastric curvature (*ypN2*). The resection margins were free, but the distance from the lesion to the anterior and retropancreatic margins was <0.5 mm.

The patient underwent adjuvant treatment with chemoradiotherapy, with capecitabine at a dose of 800 mg/m^2 twice daily (total daily dose 1600 mg/m^2) during radiotherapy (1.8 Gy/day for 5 days of treatment per week) over 5 weeks.

One month after the end of adjuvant treatment, a new PET/CT scan showed lymph node enlargement in the bilateral common iliac lymph nodes. Lymph node excision biopsy confirmed poorly differentiated metastatic carcinoma.

The patient then started treatment with gemcitabine (1000 mg/m^2 on D1, 8 and 15 every 28 days), but after the second cycle, the dose was reduced to 800 mg/m^2 D1 to D8 every 21 days due to toxicity. After 6 cycles, imaging exams demonstrated a progression of disease in the retroperitoneal lymph node, so the patient underwent Stereotactic Body Radiation Therapy (SBRT) on retroperitoneal lymph nodes.

Six months later, a new PET/CT scan showed recurrence of disease in the paraaortic chain lymph nodes, left pulmonary hilum, and left pulmonary nodule, which was also confirmed by biopsy.

We decided to return to chemotherapy with the FOLFIRINOX regimen, with an initial partial response after 4 cycles. However, after 8 cycles, new disease progression developed in the mediastinal lymph nodes and in a new nodule in the left lung.

The patient underwent SBRT on the mediastinal lymph nodes and left pulmonary nodule, with a significant reduction in metabolism after 3 months. However, after 7 months of SBRT, there was new pulmonary and mediastinal lymph node progression.

The patient subsequently was re-exposed to gemcitabine, but after 2 cycles, the treatment was suspended due to bone marrow toxicity. The patient's treatment was changed to nab-paclitaxel, but this treatment was also discontinued due to neuropathy. The treatment timeline is summarized in Figure 3.

At that time, a 315-gene Next-Generation Sequencing (NGS) panel was ordered and performed on the primary tumor, and a *BRAF V600E* mutation (p. Val600Glu/V600E) was found.

Due to the lack of standard therapies for a disease that proved resistant to the best chemotherapeutic options, the patient started off-label therapy with dabrafenib 300 mg per day in combination with trametinib 2 mg per day. One month after treatment started, due to bone marrow toxicity, the dose of dabrafenib was reduced to 225 mg and that of trametinib to 2 mg, both every other day.

Restaging PET/CT after 2 and 6 months showed partial response (Figure 4a, Figure 4b, Figure 5 and Figure 6).

After 9 months starting treatment, the patient underwent a new

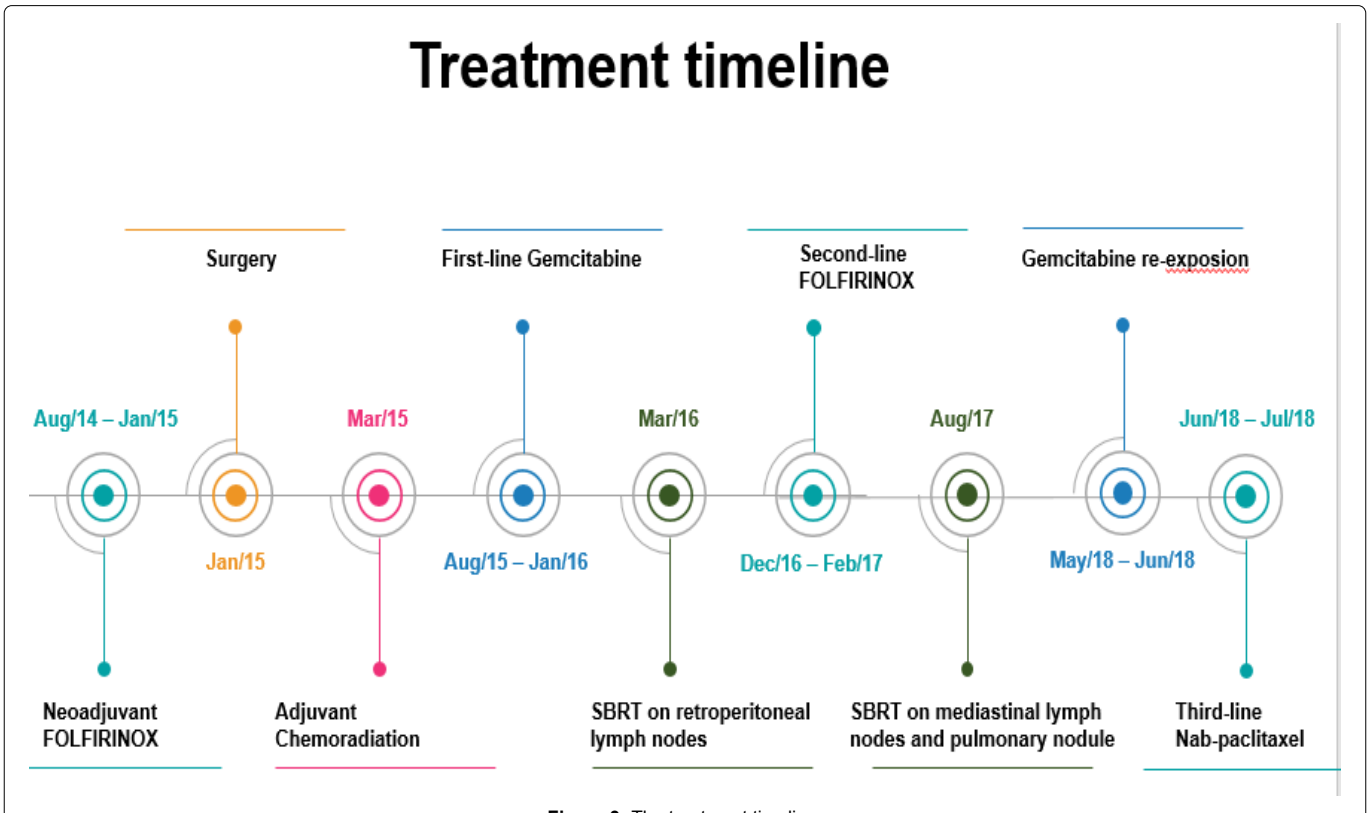

Figure 3: The treatment timeline.

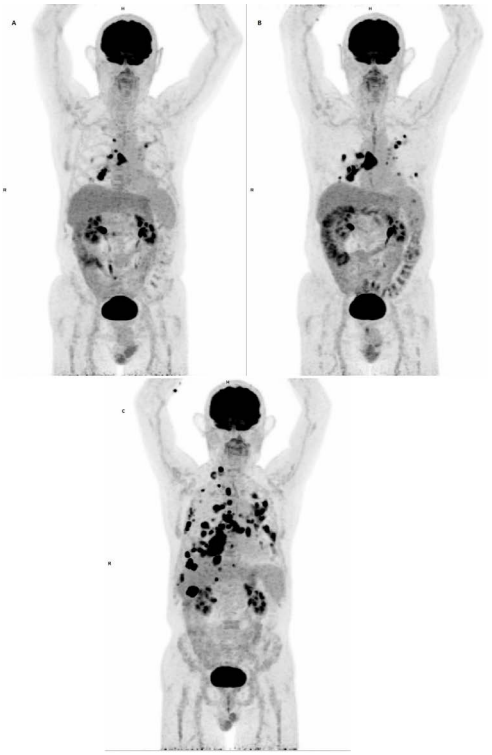

Figure 4: PET/CT-18F-FDG MIP (Maximum Intensity Projection) whole-body images; A) 6 months after starting treatment; B) pre therapy, partial response in lung and mediastinal lesions; C) Disease progression 9 months after starting treatment.

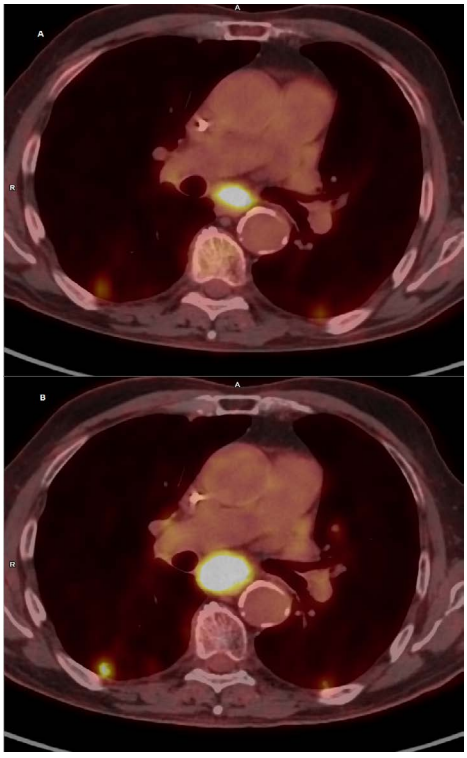

Figure 5: PET/CT-18F-FDG axial images; A) 6 months after starting treatment; B) Pre therapy, partial response in subcarinal-enlarged lymph node.

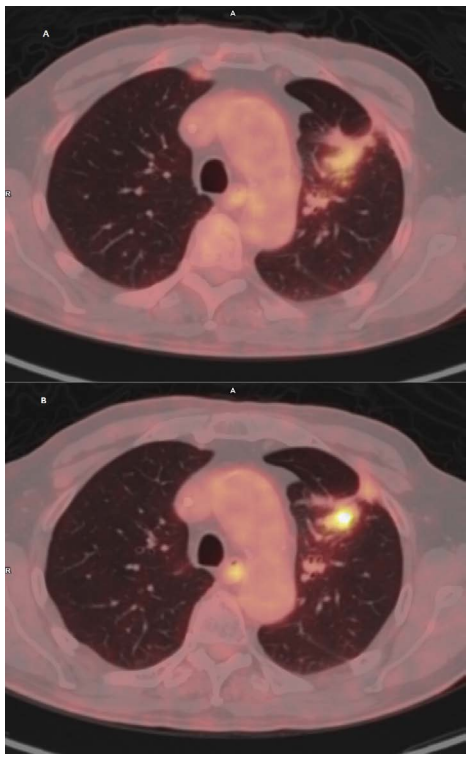

Figure 6: PET/CT-18F-FDG axial images; A) 6 months after starting treatment; B) Pre therapy, partial response in lung lesion.

chest CT scan that showed disease progression in the lung and lymph nodes (Figure 4c). At that time, treatment was suspended, and the patient died 2 months later.

Discussion

We report the case of a partial response to the combination of dabrafenib and trametinib in a patient with *BRAF*-mutated refractory metastatic PACC, and we will discuss the characteristics of pancreatic carcinomas with acinar differentiation, their molecular changes and data on treatment with *BRAF* and *MEK* inhibitors.

Not surprisingly, given the clinicopathological differences, PACC has a distinct molecular phenotype from PADC. PACC does not harbor mutations commonly found in PDAC (e.g *KRAS* and *SMAD4*), and abnormalities in p16 expression are not detected and rarely show immunoreactivity to TP53 [17,18]. These tumors also have a mutation in the Adenomatous Polyposis Coli (APC) gen e / β - c a t e n i n pathway in 20%-25% of cases, with genetic similarity to colon cancer and occasional association with patients with Familial Adenomatous Polyposis (FAP) [17]. Whole-Exome Sequencing (WES) identified rare somatic mutations in *BRAF, GNAS,* and *JAK1*, suggesting that a subset of PACC may be driven by well-characterized oncogenic events [9]. However, these alterations occur in a small proportion of tumors, and overarching genomic themes have yet to be elucidated.

The frequency of *BRAF* mutations in PACC is approximately 10%, which is a much higher rate than 2% in PADC [19,20]. Vemurafenib and dabrafenib, which are highly selective for *BRAF*-mutant cells, have been approved by the US Food and Drug Administration for melanoma therapy [21,22].

However, most patients treated with a *BRAF* inhibitor progressed within 6-8 months after starting the therapy. The relatively short duration of efficacy of *BRAF* inhibitors suggests a rapidly acquired clinical resistance, reflecting the ability of cells to bypass *BRAF* inhibition [23].

Many mechanisms of resistance to *BRAF* inhibitors have been described and are classified as *ERK*-dependent (e.g., acquired *NRAS* mutation, truncated forms of *BRAF*, overexpression of mutant *BRAF*, downstream reactivation of MEK and secondary *MAP2K* mutations), leading to *MAPK* reactivation despite *BRAF* inhibition, while others are ERK-independent (e.g., *TKR* upregulation), promoting survival through alternative pathways bypassing *ERK* [23,24].

Several other solid tumors with *BRAF* mutations have shown a benefit from combining *BRAF* and *MEK* inhibitors. Randomized phase III clinical trials have shown the superiority of *BRAF* plus *MEK* inhibitors compared with *BRAF* inhibitors alone in *BRAF*-mutant melanoma. [25] Another study of dabrafenib plus tramatenib showed more favorable responses and progression-free survival than another study with vemurafenib alone in patients with metastatic *BRAF*-mutant colorectal cancer [26]. In addition, two cases also showed a dramatic response with the combination of trametinib and dabrafenib in BRAF-mutated refractory metastatic cholangiocarcinoma [27].

Given the improved efficacy of dual *BRAF* and *MEK* inhibition in melanoma, colorectal cancer, and cholangiocarcinoma, we elected to treat our patient with *BRAF*-mutant PACC with a combination of dabrafenib and trametinib since the tumor was refractory to chemotherapy with FOLFIRINOX, gemcitabine and nab-paclitaxel. The patient used trametinib and dabrafenib with a partial response for 6 months, even with a dose reduction due to toxicity.

Several studies are currently evaluating combinations of *BRAF* and *MEK* inhibitors in non-melanoma and non-colorectal cancer BRAF-mutated tumors (NCT02034110, NCT03543306, NCT01336634, NCT03244956, NCT03975231, NCT02124772). Additional data from these prospective clinical trials will help confirm the activity of dual MEK/BRAF inhibition as a standard approach in *BRAF*-mutant PACC.

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Conflict of Interest: Author Allan Andresson Lima Pereira has received speaker honorarium from Novartis. Author Gustavo S. Fernandes has received a speaker honorarium and advisory board fees from Novartis. Other authors declare that they have no conflict of interest.

Authors' contributions: All authors above contributed to conception and design, acquisition of data, drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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Author Affiliations

Top

[1]*Division of Medical Oncology, Hospital Sirio-Libanês, Brasília-DF, Brazil*

[2]*Division of Pathology, Hospital Sírio-Libanês, São Paulo-SP, Brazil*

[3]*Division of Nuclear Medicine, Hospital Sírio-Libanês, Brasília-DF, Brazil*

[4]*Universidade de Brasília, Brasília-DF, Brazil*