

# Uptake of $^{99m}\text{Tc}$ -MIBI by Sclerosing Pneumocytoma Raising a False Suspicion of Metastasis From Medullary Thyroid Carcinoma

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Technetium-99m methoxy isobutyl isonitrile ( $^{99m}\text{Tc}$ -MIBI; sestamibi) single-photon emission computed tomography (SPECT)/computed tomography (CT) performed for preoperative localization of parathyroid adenomas or for other indications can reveal incidentalomas. Interpretation of such findings can be challenging, particularly when thyroid or other endocrine tumors are also present. Preoperative staging of a 59-year-old female patient with medullary thyroid carcinoma (MTC) showing moderate hypermetabolism on  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/CT also detected a slightly hypermetabolic pulmonary nodule (standardized uptake value normalized by body weight  $\text{max} = 2.0 \text{ g/mL}$ ). A sestamibi SPECT/CT performed because of concomitant primary hyperparathyroidism showed increased uptake by both the MTC and the pulmonary nodule, raising suspicion of MTC metastasis. Lung wedge resection biopsy revealed a sclerosing pneumocytoma (SPC), a rare benign pulmonary tumor not previously known to retain sestamibi. In contrast to classical knowledge that sestamibi uptake by tumors is associated with its retention by mitochondria, immunohistochemical analyses showed that the mitochondrial content of the patient's SPC was low. This case illustrates the behavior of SPC in sestamibi scintigraphy and indicates that SPC is a potential cancer mimicker in this setting.

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**Freeform/Key Words:**  $^{18}\text{F}$ -FDG PET/CT,  $^{99m}\text{Tc}$ -MIBI, medullary thyroid carcinoma, mitochondria, sclerosing pneumocytoma

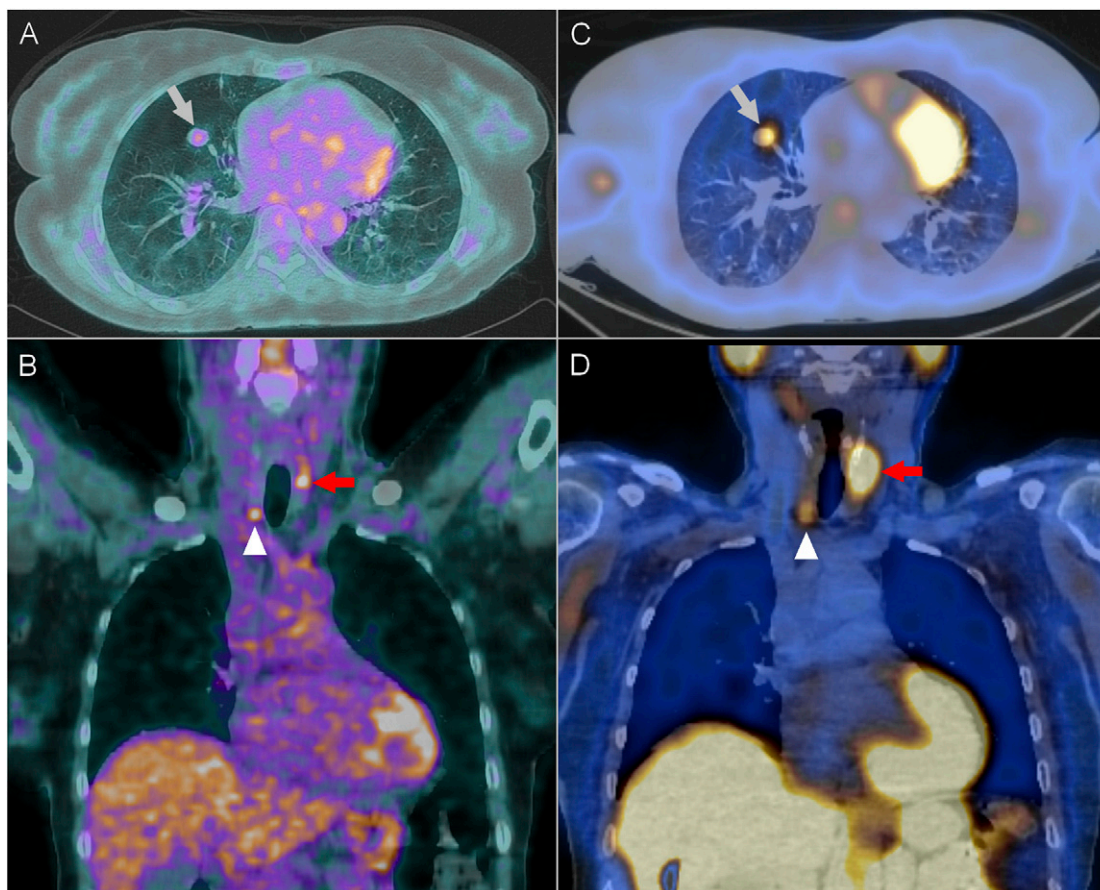
Technetium-99m methoxy isobutyl isonitrile ( $^{99m}\text{Tc}$ -MIBI; sestamibi) single-photon emission computed tomography (SPECT)/computed tomography (CT) is a high-accuracy modality for the localization of parathyroid adenomas [1]. Incidental findings are frequent during sestamibi scans and mainly include nodular uptake in the thyroid gland. The presence of a thyroid nodule with a sestamibi-hot and  $^{99m}\text{Tc}$ -cold phenotype is suspicious for malignancy and may warrant fine-needle aspiration before parathyroid adenoma resection. Interestingly, sestamibi imaging has also shown potential for predicting malignancy of pulmonary lesions with high (>80%) sensitivity and specificity, as confirmed by a recent meta-analysis [2]; therefore, some experts have suggested this imaging modality as a potential alternative to  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET)/CT, particularly in

Abbreviations:  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -fluorodeoxyglucose;  $^{99m}\text{Tc}$ -MIBI sestamibi, technetium-99m methoxy isobutyl isonitrile; CEA, carcinoembryonic antigen; CT, computed tomography; MEN2, type 2 multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; PET, positron emission tomography; SPC, sclerosing pneumocytoma; SPECT, single-photon emission computed tomography.

countries where access to the latter is limited because of higher costs. We present the case of a female patient diagnosed with medullary thyroid carcinoma (MTC) and primary hyperparathyroidism, in whom pulmonary metastasis was suspected in part because of increased sestamibi uptake by a pulmonary nodule, similar to the primary MTC lesion. Lung wedge resection biopsy showed sclerosing pneumocytoma (SPC), a rare benign pulmonary tumor whose biological behavior on sestamibi scintigraphy has never been reported.

## 1. Case Presentation

A 59-year-old Caucasian female underwent  $^{18}\text{F}$ -FDG PET/CT for follow-up of invasive localized breast cancer, previously treated by surgery and adjuvant radiotherapy. A 13-mm nodule was detected in the right lung, exhibiting slight FDG uptake (standardized uptake value normalized by body weight max = 2.0 g/mL) (Fig. 1A). A moderately hypermetabolic (standardized uptake value normalized by body weight max = 3.7 g/mL) 14-mm nodule was also visualized in the upper left thyroid lobe (Fig. 1B). Increased levels of serum calcitonin (377 ng/L) and carcinoembryonic antigen (CEA) (16.6  $\mu\text{g/L}$ ) suggested MTC, subsequently

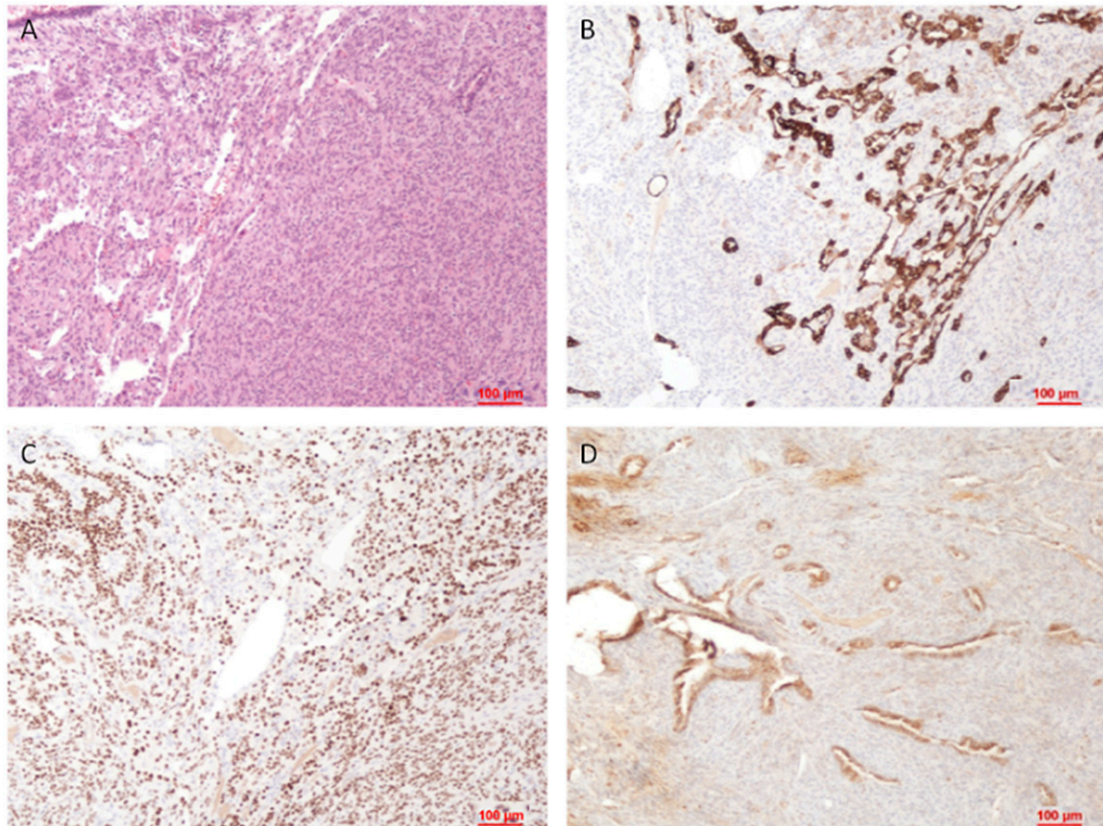


**Figure 1.**  $^{18}\text{F}$ -FDG PET/CT and  $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT images. (A)  $^{18}\text{F}$ -FDG PET/CT performed for staging of a resected localized breast cancer revealed a slightly hypermetabolic right pulmonary lesion (arrow). (B)  $^{18}\text{F}$ -FDG PET/CT also showed two cervical sites of focal uptake, one in the upper pole of the left thyroid lobe (red arrow) and the other posterior to the lower pole of the right thyroid lobe (white arrowhead), confirmed on histology to correspond to MTC and parathyroid adenoma, respectively. (C, D) On sestamibi SPECT/CT imaging, both (C) the pulmonary lesion (white arrow) and (D) the fine-needle aspiration cytology-confirmed MTC (red arrow) exhibited increased uptake, as did the right parathyroid adenoma (white arrowhead).



confirmed by fine-needle aspiration cytology. Family history was notable for breast and colorectal cancer in different second-degree relatives from the paternal side but was negative for MTC, primary hyperparathyroidism, and pheochromocytoma. While awaiting the results of germline *RET* gene sequencing for type 2 multiple endocrine neoplasia (MEN2) syndrome, biochemical screening excluded pheochromocytoma but revealed primary hyperparathyroidism. Cervical ultrasonography and sestamibi SPECT/CT (extending to the level of the chest and the upper abdomen to detect any potential ectopic parathyroid adenomas) localized a right inferior parathyroid adenoma. Both the fine-needle aspiration cytology–confirmed MTC (Fig. 1D) and the pulmonary nodule (Fig. 1C) exhibited increased  $^{99m}\text{Tc}$ -MIBI uptake. Surgical resection of the pulmonary nodule was thus proposed to exclude MTC pulmonary metastasis, even though solitary MTC pulmonary metastasis is rarely seen in the absence of cervical lymph node involvement. Histopathologic analysis of the excised nodule revealed SPC, a rare benign pulmonary tumor (Fig. 2).

After exclusion of pulmonary metastasis of MTC, total thyroidectomy and prophylactic central neck lymph node dissection were performed, along with resection of the parathyroid adenoma. Interestingly, the thyroid specimen did not reveal histologic signs in favor of MEN2; notably, there was no C-cell hyperplasia. Biochemical response was rapid, with normalization of serum calcitonin and CEA levels. Sequencing of the *RET* and *BRCA-1/BRCA-2* genes on genomic DNA extracted from peripheral blood did not reveal pathogenic



**Figure 2.** Histologic images of the pulmonary lesion. (A) The pulmonary lesion was predominantly solid with round and atypical spindle stromal cells. Focally, epithelial cells with papillary growth pattern and areas of sclerosis were present. (B) Cytokeratin (CK) immunostaining was positive only in the epithelial cells. (C) Thyroid transcription factor 1 immunostaining showed nuclear reactivity in both stromal and epithelial cells, a typical finding in SPC. Similar to CK, napsin A was expressed only in epithelial cells (not shown). (D) Immunostaining for mitochondrial antigen [3] showed relatively poor mitochondrial content in neoplastic cells. Scale bar = 100  $\mu\text{m}$ .

alterations. For the *RET* gene in particular, polymerase chain reaction and sequencing of coding exons 5, 8, 10, 11, and 13 to 16 and the respective splicing regions were performed (reference sequence NG\_007489.1, LRG\_518t1), according to published guidelines and local practices. At 1-year follow-up, the patient was disease free with undetectable serum calcitonin level, normal serum CEA level (<5 µg/L), and no suspicious cervical lymph nodes on ultrasonography. Primary hyperparathyroidism resolved as well, and the breast cancer continues to be in complete remission.

## 2. Discussion

Sestamibi imaging, initially implemented for cardiac scintigraphy, has become a mainstay of the preoperative localization of parathyroid adenomas, frequently allowing for targeted, minimally invasive surgery, as well as offering the ability to localize ectopic adenomas or diagnose multiglandular disease [1]. Additional interest has been drawn to its potential for predicting malignancy of thyroid and pulmonary lesions. For instance, a direct comparison of sestamibi SPECT/CT vs <sup>18</sup>F-FDG PET/CT in a prospective study showed similar accuracy in the diagnosis of pulmonary malignancies [4]. Moreover, the use of sestamibi SPECT for staging of thyroid malignancies has been suggested for differentiated thyroid carcinoma [5] and interestingly also for MTC, with better performance than conventional CT in the assessment of neck and chest involvement during staging for recurrent MTC [6]. In this context, the sestamibi-positive pulmonary lesion of our patient warranted excision biopsy to exclude MTC metastasis; however, histopathologic examination showed SPC, a rare benign tumor previously known as sclerosing hemangioma [7].

SPC typically presents as a solitary incidental nodule, mostly asymptomatic and with predominant incidence in women (female/male ratio, 5:1). Incidental diagnosis of SPC in various radiologic and nuclear medicine studies has been recently reported [8]. SPC usually demonstrates low-to-moderate hypermetabolism on <sup>18</sup>F-FDG PET, as was the case in our patient, with uptake proportional to tumor size. To the best of our knowledge, there are no previous reports on the behavior of SPC on sestamibi imaging. Although false-positive findings of sestamibi uptake in pulmonary nodules have been described, data on the exact histopathologic nature of the misleading lesions are scarce. In one of the few publications providing detailed reports of benign lesions with sestamibi uptake [9], the majority (9 of 10) were infectious (abscesses, tuberculosis, hydatid cysts) or inflammatory (granulomatosis) lesions, with only one benign tumor (hamartoma). Discovery of an SPC in this setting has never been reported.

In addition, we attempted to clarify the mechanism of increased sestamibi avidity of SPC. Sestamibi is a lipophilic, cationic isonitrile compound that diffuses passively across cell membranes. Because of its negative transmembrane potential, it is primarily sequestered in the mitochondria and thereby trapped intracellularly. Mitochondria-rich oxyphil cells have accounted for the increased retention of sestamibi by parathyroid adenomas [1]. Thus, we hypothesized that the avidity of the patient's SPC for sestamibi would be linked to a high mitochondrial content. The latter was previously documented in the cytoplasm of epithelial (surface) cells of four SPCs studied with electron microscopy [10]. Nevertheless, immunostaining using a monoclonal antimitochondrial antigen antibody [3] revealed a rather low mitochondria content in the patient's SPC (Fig. 2D). Alternatively, increased vascularity of SPC may explain its avidity to sestamibi. In support of this hypothesis, studies assessing the role of sestamibi in the investigation of myocardial ischemia have shown that its uptake is indeed proportional to blood flow [11].

On the basis of *RET* gene sequencing results, which included all the coding exons recommended by the latest American Thyroid Association guidelines [12], we concluded that the patient most probably had sporadic MTC. This conclusion was also supported by the negative family history for MEN2 manifestations, the absence of C-cell hyperplasia in the patient's thyroid, and the relatively advanced age of the patient for a first manifestation of

MEN2-associated MTC. Thus, we believe that a phenocopy is more likely than a mutation in another region of the *RET* gene or a mutation in another unknown gene associated with MTC.

In conclusion, endocrinologists and nuclear medicine physicians should be aware that sestamibi imaging can be accompanied by incidental pulmonary findings, which can raise suspicion of metastasis in the context of MTC, whether sporadic or associated with MEN2. SPC is a rare but increasingly reported cancer mimicker in this context, and it should be considered in the differential diagnosis along with inflammatory and infectious processes.

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**Disclosure summary:** The authors have nothing to disclose.

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