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Coincidental visualization of an atypical bronchial carcinoid on Tc-99m-sestamibi scan in Kallmann's syndrome

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We report a case of an atypical bronchial carcinoid showing sestamibi uptake. A 27-year-old man with Kallmann's syndrome and hyperparathyroidism had parathyroid scintigraphy with ^{99m}Tc-sestamibi. A focal uptake was observed on the right perihilar region, and this right perihilar mass was demonstrated on computed tomography and proved histologically to be an atypical bronchial carcinoid tumor. Factors which may explain the tumoral avidity for sestamibi are increased blood flow, transmembrane potentials of plasma and mitochondrial membranes and the relative number of mitochondria present in the cells of this carcinoid tumor. The importance of this case is the coincidence of an atypical carcinoid in a patient with significant failure of secondary sexual characteristics, right renal agenesis and bilateral anosmia associated with Kallmann's syndrome.

Key words: ^{99m}Tc-sestamibi, carcinoid, Kallmann's syndrome

INTRODUCTION

BRONCHIAL CARCINOID TUMORS USUALLY are benign and have a good prognosis with a low incidence of metastases, but some run a rapid course with metastatic spread and are histologically labeled as atypical carcinoid tumors.[1,2] Kallmann's syndrome is isolated gonadotropin deficiency, or idiopathic hypogonadotropic gonadotropin deficiency manifests itself as a defect in the synthesis or release of luteineizing hormone releasing hormone (LHRH). An association between carcinoids and multiple endocrine neoplasia (MEN) has been shown previously.[3,4] But there are no data available on carcinoid tumors associated with Kallmann's syndrome.

Although developed as an agent for myocardial perfusion imaging, several studies have shown that ^{99m}Tc-sestamibi accumulates in viable tumor tissue, including thyroid,[5,6] breast,[7] lung cancers,[8] lymphomas[9] and musculoskeletal sarcomas.[10] There are also case reports describing uptake in carcinoid tumors.[11–13]

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CASE REPORT

A 27-year-old man with Kallmann's syndrome and hyperparathyroidism was referred to the department of nuclear medicine in our hospital for scintigraphic evaluation of possible parathyroid pathology. The patient showed significant failure of the secondary sexual characteristics, right renal agenesis and bilateral anosmia associated with Kallmann's syndrome. On physical examination, the patient had hemiplegia of the right upper extremity and shortening of the left lower extremity which were thought to be the sequeles of polio suffered at the age of 4 years. He had also pectus carinatum deformity, decreased breath sounds in the lower lobe of the right lung and significant failure of the secondary sexual characteristics. Biochemical analysis revealed high blood levels of BUN (40 mg/d*l*; normal range (NR): 8–25 mg/d*l*), creatinine (2.0 mg/d*l*; NR: 0.9–1.6 mg/d*l*), parathormone (218 pg/m*l*; NR: 12–72 pg/m*l*) and alkaline phosphatase (652 U/*l*; NR: 50–305 U/*l*). Chest radiograph showed an irregular opacity 3 × 4 cm in size at the hilus of the right lung. Abdominal computed tomography (CT) showed right renal agenesis,

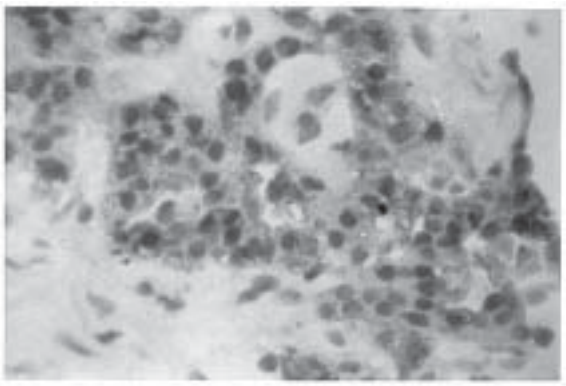

Fig. 1 Immunohistochemically, the tumor cells showed strong positivity for chromogranin A. Although no mitotic activity was noted, extensive necrosis supported the diagnosis of atypical carcinoid tumor.[14]

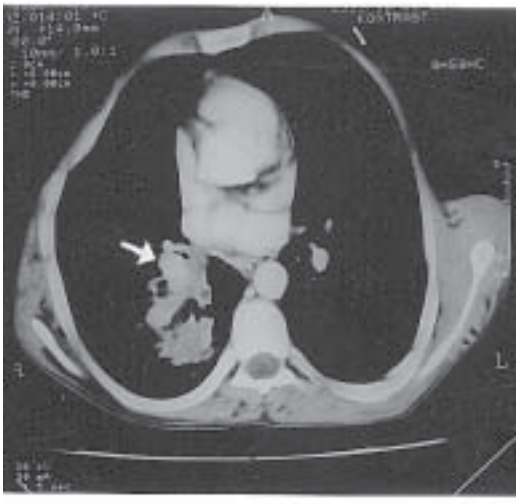

Fig. 2 CT examination shows right subhilar peribronchial infiltration spreading through right lower lobe bronchus. The borders of the mass cannot be identified from the adjacent atelectasis.

anatomic variation on the uncus of the pancreas, compensatory changes in the left kidney and generalized osteoporosis.

With 370 MBq (10 mCi) of Tc-99m-sestamibi, the parathyroid scintigraphy was performed by means of a Starcam 4000i gamma camera (GE Medical Systems, Milwaukee, USA) equipped with a pinhole collimator for early images and a parallel hole collimator for late images. Early and late images were obtained 15 min and 180 min postinjection, respectively. An early sestamibi image showed homogeneous radiopharmaceutical uptake in the thyroid tissue. On the late image, a pathological focal uptake in the right thoracic area was visualized, but the thyroid activity had decreased. Thoracic CT showed a mass in the hilus of the right lung the borders of which could not be distinguished from the adjacent atelectasis. A bronchoscopic fine needle aspiration biopsy was done for the hilar mass. Microscopic examination revealed an insular pattern of small, uniform cells with neuroendocrine features and areas of necrosis. Immunohistochemically, the tumor cells showed positivity for chromogranin A (Fig. 1). Although no mitotic activity was noted, extensive necrosis supported the diagnosis of atypical carcinoid tumor.[14]

DISCUSSION

Nuclear medicine techniques based on the visualization of specific functions offer several advantages over the other imaging methods for tumor detection. If a highly specific radiopharmaceutical is available, a tumor may be depicted on the basis of its biochemical, physiological or biological characteristics. Anatomical deterioration, which may cause problems in evaluating CT and MRI, will not disturb interpretation in nuclear medicine but an ideal tumor depicting agent for nuclear medicine does not yet exist, though it has been searched for. In the diagnostic investigation of neural crest tumors, radioiodinated metaiodobenzylguanidine (MIBG) scintigraphy is the principal imaging method. But, it still plays a limited role in the detection of carcinoids. The literature shows that approximately 50–60% of carcinoids are able to concentrate MIBG.[15] Neuroendocrine tumors are also cases for the somatostatine analogue [^{111}In-DTPA-D-Phe^{1}]-octreotide (Octreoscan), though later reports have claimed that it is also useful for the detection of more common tumors such as breast carcinoma and lymphoma, as well as in inflammatory and autoimmune diseases.[16] Carcinoid tumors radiologically manifest as hilar or perihilar masses, with or without associated atelectasis, pneumonia, bronchiectasis, or mucoid impaction.[17] In this case, the perihilar mass was associated with distal atelectasis and/or pneumonic infiltration which was not delineated sharply from the tumor (Fig. 2). This is not a specific finding for carcinoid tumors because all endobronchial-growing tumors, benign or malignant, may cause partial or total obstruction of the bronchial tree, causing distal atelectasis or pneumonia.

^{99m}Tc-hexakis-2-methoxyisobutyl isonitrile (sestamibi) is an excellent myocardial perfusion agent. Since the early 1990s, an increasing number of papers have appeared describing the uptake of sestamibi in tumors. Since the incidental finding of a pulmonary metastasis from thyroid carcinoma during cardiac imaging,[18] sestamibi uptake has been reported in lung cancers,[8] breast carcinoma,[7] lymphoma,[9] peripheral soft tissue and bone sarcomas[10] and parathyroid carcinoma[19] as well as medullary thyroid carcinoma[20] of the thyroid. The augmented uptake in malignant tumors is believed to be caused by stronger negative mitochondrial and plasma membrane potentials secondary to increased metabolism of tumor cells.[21,22] Indirect mechanisms, such as an increase in blood flow and capillary permeability, have also been suggested.[23]

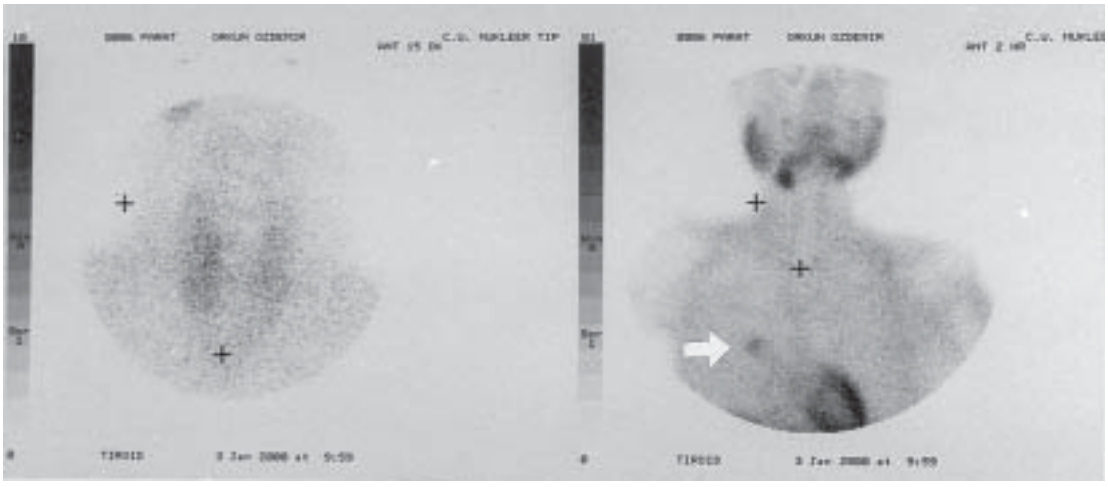

Fig. 3 Tc-99m-sestamibi images taken for a possible parathyroid pathology are shown on this figure. Early sestamibi image shows homogeneous radiopharmaceutical uptake in the thyroid tissue. On the late image using the parallel hole collimator, a pathological focal uptake on the right thoracic area is visualized, while the thyroid activity is decreased. These findings were evaluated as normal for thyroid and parathyroid glands. A focal radiopharmaceutical uptake on the right perihilar region is seen on the delayed image (right side). This appearance was histopathologically shown to be an atypical bronchial carcinoid tumor.

The equilibrium intracellular concentration of sestamibi has been shown to be inversely related to the degree of expression of P-glycoprotein, an ancient pump protein responsible for the development of multi-drug resistance to chemotherapeutic agents.[24]

Sestamibi is an agent which also localizes the benign tumors, and it is used for the detection and localization of parathyroid adenoma with a sensitivity exceeding 95%.[25] Nevertheless, dual-phase parathyroid imaging with sestamibi may fail to detect glands weighing less than 500 mg, and lesions of the thyroid, such as adenomas and carcinomas, may interfere with the interpretation of parathyroid pathology findings.[26] The sensitivity for hyperplastic tissue is low at below 50%.[25]

Because bronchial carcinoids are particularly slow growing, resection generally leads to an excellent prognosis.[27] In the case of typical carcinoids, a review of 60 patients suggests that long-term survival is as high as 89.6% at 10 years.[28] In contrast, atypical carcinoids had a significant malignant potential with a 10-yr survival of 60%. Negative prognosis related to lymph node metastases has been reported by many authors.[28,29]

In the literature there are case reports describing sestamibi uptake in thymic and bronchial carcinoids.[12,13,30,31] Desai and Yuille[11] also reported a case of atypical bronchial carcinoid with bone metastasis in which both primary and metastatic lesions had concentrated sestamibi. In a previous reported case of a patient with MEN type I, the two components of the disease, hyperplastic parathyroid gland and pituitary adenoma, and also a thymic carcinoid were seen on a sestamibi scan.[16] Possible factors which may explain the tumoral avidity for sestamibi are increased blood flow, transmembrane potentials of plasma and mitochondrial membranes and the relative number of mitochondria present in the cells of this carcinoid tumor.

The association of MEN and carcinoids have been described in the literature.[3,4] Most patients with carcinoids and hyperparathyroidism (82%) have had parathyroid hyperplasia or multiple parathyroid adenomas.[3] Hyperparathyroidism was the presenting abnormality in our present case as an indication for a parathyroid scintigraphy. Sestamibi scan (Fig. 3) did not reveal any pathological accumulation at the neck, but a focal pathological uptake was seen in the right thoracic area which was then histopathologically proven to be an atypical carcinoid tumor. Because of the patient's self discharge, further evaluations of the association of bronchial carcinoid with hyperparathyroidism and MEN could not be performed.

Idiopathic hypogonadotrophic hypogonadism (Kallmann's syndrome) was briefly described as male hypogonadism with anosmia or hyposmia.[32] The disorder is inherited as an X-linked recessive trait or an autosomal dominant trait with variable expressivity. The defect appears to be in the synthesis or release of LHRH. Serum FSH and LH levels are usually below the normal range, and plasma testosterone levels are low for age. Genital, somatic, and neurological abnormalities may also be present. In the present case, coexisting defects were cryptorchidism, microphallus, anosmia and renal agenesis. According to our review, the literature does not contain any report describing an association between Kallmann's syndrome and both typical and atypical carcinoid tumors.

The main importance of this case is to show the possibility of an atypical carcinoid tumor existing in a patient with Kallmann's syndrome. The incidental localization of the carcinoid during parathyroid scintigraphy is another interesting issue. These findings have changed the management of the patient remarkably, causing high suspicion of malignancy. The sestamibi uptake has led to a follow-up CT scan and eventually biopsy of the lesion. Although sestamibi is a nonspecific agent and reflects metabolic activity, it detected the carcinoid tumor successfully in our present case. The reported case shows that sestamibi scintigraphy may be useful in finding possible coexisting tumors in hyperparathyroidism, such as carcinoid tumors or lesions related to MEN.

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