

Recurrent thymic carcinoid tumor in familial isolated primary hyperparathyroidism

Jeong Eun Song¹, Mu Hyun Shon¹, Ga Young Kim¹, Da Young Lee¹, Jung Hun Lee¹, Jong Ho Kim²,
Ho Sang Shon³, Ji Hyun Lee³, Eon Ju Jeon³, Eui Dal Jung³

¹Department of Internal Medicine, Catholic University of Daegu School of Medicine; ²Department of Internal Medicine, Kyungpook National University School of Medicine; ³Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, Korea

Familial isolated primary hyperparathyroidism (FIPH) is associated with multiple endocrine neoplasia type 1 (MEN1) syndrome, primary hyperparathyroidism accompanied by jaw-tumor syndrome, and familial hypocalciuric hypercalcemia. FIPH may be an early stage of MEN1 or an allelic variant of MEN1. Thymic carcinoid tumor is a rare tumor in MEN1 syndrome. Here, the authors report the case of a 40-year-old man diagnosed with recurrent thymic carcinoid tumor and FIPH. Both the patient and his elder sister had been previously diagnosed to have FIPH with a novel frameshift mutation in the MEN1 gene. Initially, the patient underwent thymectomy because of an incidental finding of a mediastinal mass in his chest X-ray, and had remained asymptomatic over the following 4 years. Pancreas computed tomography conducted to evaluate MEN1 syndrome revealed anterior and middle mediastinal masses, and resultantly, massive mass excision was performed. Histological findings disclosed atypical carcinoids with infiltrative margins. In view of the thymic carcinoid tumor relapse that occurred in this patient, the authors recommend that regular pancreas and pituitary imaging studies be conducted for FIPH associated with a MEN1 gene mutation.

Keywords: Hyperparathyroidism; Carcinoid tumor; Multiple endocrine neoplasia type 1

INTRODUCTION

Primary hyperparathyroidism (PHPT) is usually non-familial [1], but approximately 10% of cases manifest as multiple endocrine neoplasia types 1 (MEN1) or 2 (MEN2), familial hypocalciuric hypercalcemia, PHPT-jaw tumor (JT) syndrome, or familial isolated primary hyperparathyroidism (FIPH) [2]. FIPH is defined as hereditary PHPT without involvement of other diseases or tumors, and occurs as an early manifestation of MEN1 or of an allelic variant of the MEN1 gene [3]. Thymic carcinoid tumors are rare neuroendocrine tumors with a prevalence of 2.6 to 5% in MEN1 [4]. Thymic carcinoid tumor is usually

encountered in men (93%) of mean age 43 years at diagnosis [5]. When it occurs in MEN1, this carcinoid tumor shows more aggressive patterns, such as, tissue invasion and distant metastasis, than sporadic thymic carcinoid tumor. In this report, we present a case of a recurrent thymic carcinoid tumor in FIPH with a novel MEN1 gene mutation.

CASE

In 2012, a 40-year-old man was admitted to our hospital for surgery of a recurrent carcinoid tumor. In 2004, he had been diagnosed to have a thymic carcinoid tumor, which was detected by health-screen chest computed tomography. At that time, his serum calcium was elevated, but not further evaluated. In 2007, his older sister had been diagnosed with papillary thyroid cancer, and during preoperative evaluation, had been diagnosed to have PHPT with multiple parathyroid involvement.

On admission serum calcium and parathyroid hormone (PTH) levels were checked to evaluate familial hyperparathyroidism.

Received: September 25, 2013, Revised: October 17, 2013,
Accepted: October 18, 2013

Corresponding Author: Eui Dal Jung, Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine, Catholic University of Daegu School of Medicine, 33 gil 17 Duryugongwon-ro, Nam-gu, Daegu 705-718, Korea
Tel: +82-53-650-4218, Fax: +82-53-651-4009
E-mail: jed15@cu.ac.kr

His serum calcium and phosphate levels were 11.7 and 2.4 mg/dL, respectively, and his intact PTH (iPTH) level was 136.3 pg/mL. He also was diagnosed as having PHPT. Neck ultrasound examinations were carried out using a commercially available scanner equipped with a 12-MHz transducer (HD11, Philips Medical Systems, Eindhoven, the Netherlands), and multiple parathyroid nodules were detected in parathyroid glands. Parathyroidectomy was performed, and subsequent parathyroid pathology showed parathyroid hyperplasia in multiple parathyroid glands (Fig. 1). Based on clinical findings and the patient's family history, FIPH was diagnosed.

MEN1 gene mutation was evaluated as a possible genetic etiology of FIPH, and direct sequencing detected a novel frameshift mutation in exon 10 of the MEN1 gene in both the patient and his older sister. Both were then screened by abdominal computed tomography (CT) and pituitary magnetic resonance imaging (MRI) for pituitary and pancreas lesions. An anterior mediastinal mass, suspected to be a thymic tumor, was detected in an abdominal CT chest-slice (Fig. 2), but pituitary MRI revealed no mass lesion. Based on his thymic carcinoid tumor operation history, the mass was presumed to be a recurrent thymic carcinoid tumor. Surgery was recommended, and the patient was admitted to our Chest Surgery Department for a thymic tumor operation. The results of his preoperative biochemical tests were as follows: serum calcium, 9.4 mg/dL (reference range, 8.2-10.2 mg/dL); albumin, 3.7 g/dL (reference range, 3.5-5.1 g/dL); inorganic phosphate, 4.7 mg/dL (reference range, 2.5-4.5

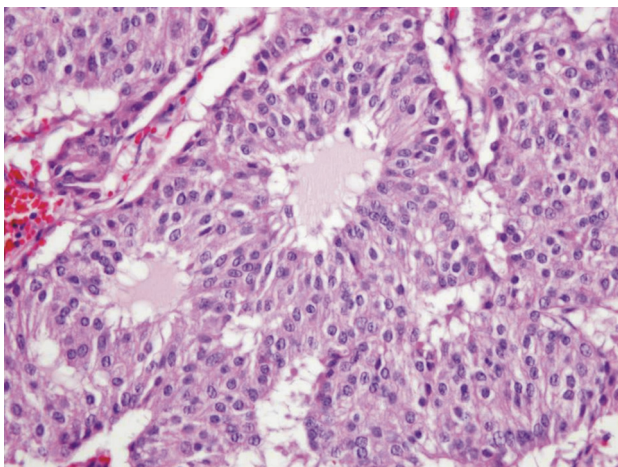


Fig. 1. Histologic findings of the parathyroid gland showing diffuse chief cell hyperplasia. Individual cells had centrally located round to oval nuclei and abundant eosinophilic cytoplasm and were arranged in tubular or solid nest patterns (H&E stain, ×400).

mg/dL); and iPTH, 3.0 pg/mL (reference range, 12-72 pg/mL). In addition, we also measured the levels of relevant hormones, but there were no abnormal findings (results are summarized in Table 1). Two tumor pieces were obtained for light microscopy and immunohistochemistry pathological studies. Grossly, the tumor was a light brown encapsulated mass measuring 7.5×5.5×4 cm. Histopathologically, the tumor had tubular or solid nest patterns and an infiltrative margin (Fig. 3) and a mitotic index of 3 high-power fields.

Immunohistochemical study revealed that tumor tissues were positive for; CD 56, neurone-specific enolase, chromogranin, and synaptophysin. The Ki67 labeling index was 5%. Accordingly, the mediastinal tumor was diagnosed as an atypical carcinoid tumor. The tumor was not totally removed because of adjacent organ invasion. Postoperatively, radiation therapy was administered to the residual tumor, and at last follow-up (12 months postoperatively) no change in tumor size was noted.

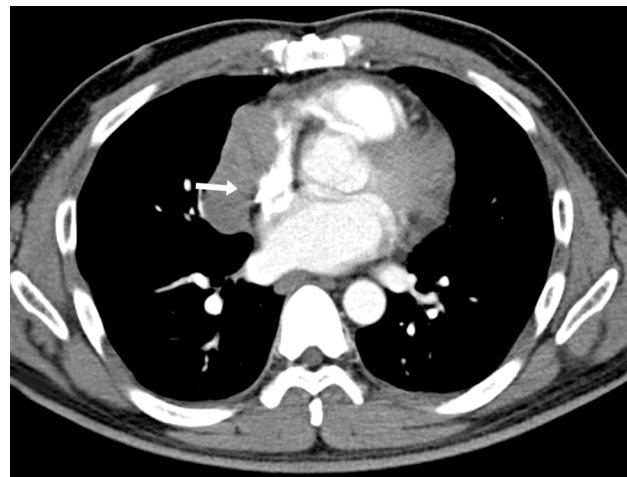


Fig. 2. Enhanced abdominal computed tomography image showing a soft tissue mass (arrow) in middle mediastinum.

Table 1. Endocrinological data

Hormone	Measured level	Reference
IGF-1 (ng/mL)	220.4	140-405
TSH (μIU/mL)	1.22	0.40-4.7
T3 (ng/mL)	1.33	0.6-1.7
fT4 (ng/mL)	1.34	0.8-1.9
Prolactin (ng/mL)	15.43	1.5-25
Epinephrine (ng/mL)	0.050	0.0-0.3
Norepinephrine (ng/mL)	0.111	0.0-0.8
Dopamine (ng/mL)	0.864	0.0-0.2
Gastrin (ng/mL)	29.0	<90

IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone; T3, Triiodothyronine; fT4, free thyroxine.

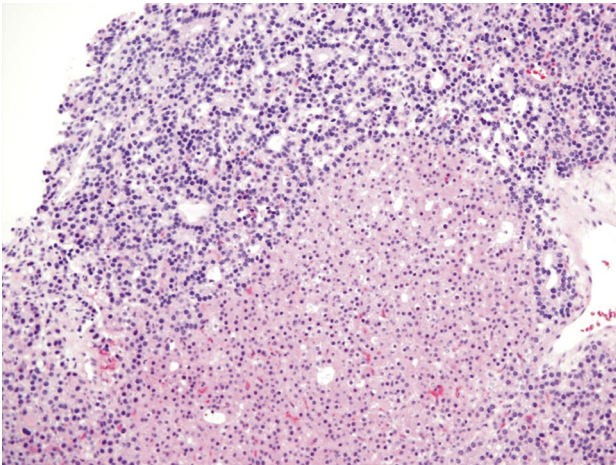


Fig. 3. Histologic findings of carcinoid tumor. Tumor cells had uniform cuboidal nuclei and eosinophilic cytoplasm and were arranged in tubular or solid nest patterns (H&E stain, ×200).

DISCUSSION

In the described case, a thymic carcinoid tumor recurred in FIPH. These tumors originate from foregut, are relatively rare, and are usually non-functioning tumors that are detected incidentally because they do not present as carcinoid syndrome and are asymptomatic [6]. Carcinoid tumors are associated with MEN1, in which they have a prevalence of 2.6 to 5%, and show a male predilection (93%) and a mean onset at age 43 years [4]. Thymic carcinoid tumor is known to have high rates of metastasis and recurrence. Pleura is a frequent site of recurrence and distant metastasis to brain is common [7]. Thymic carcinoid tumors associated with MEN1 have a poorer prognosis than the sporadic form, because they more frequently show extra-thymic invasion, distant metastasis, and recurrence after operation [8]. Furthermore, recurrent thymic carcinoid tumors are among the most common causes of death from MEN1, and as yet, they cannot be effectively treated. Teh et al. [9] recommended chest CT or MRI for the early diagnosis of thymic carcinoid tumors, and prophylactic thymectomy during parathyroidectomy in MEN1 patients.

In the described case, the recurrent thymic carcinoid tumor exhibited an aggressive pattern and had invaded the heart, and thus, complete removal was not possible. The disease may have been caused by a MEN1 gene mutation, as germline mutations usually result in MEN1 [12], although our patient was not a MEN1 patient. Our patient showed a novel frameshift mutation in the MEN1 gene. This gene is localized to human chromosome

11q13 and consists of 10 exons that encode a 610-amino acid nuclear protein, a MEN1, which participates in transcriptional regulation, genome instability, cell division, and cell proliferation [10, 11]. Lemos et al. [12] identified 1,336 MEN1 sequence abnormalities (1,133 germline mutations and 203 somatic mutations) in the National Center for Biotechnology Information PubMed literature database. Furthermore, the majority of mutations identified were nonsense and frameshift mutations, which predict premature protein truncation.

FIPH may be an early stage of MEN1 or an allelic variant of MEN1. Familial hyperparathyroidism belongs to a clinically and genetically heterogeneous group of disorders, which include MEN1, MEN2, familial hypocalciuric hypercalcemia, PHPT-JT syndrome, and FIPH. Hannan et al. [13] recommended that a MEN1 gene mutation test be performed promptly on PHPT patients that have first-degree relatives with PHPT or hypercalcemia. We examined the MEN 1 gene mutation, because our patient did not exhibit the clinical manifestations of PHPT-JT syndrome, and in so doing identified a new frameshift mutation in our patient and his older sister. In fact, several mutations of the MEN1 gene have been reported in PHPT patients [6,11]. Imaging studies failed to reveal any pancreatic or pituitary mass lesion in our patient or his sister, and pancreatic and pituitary hormone test results were normal in both. However, because they were positive for MEN1 frameshift mutation, follow up imaging and hormone tests were instituted to monitor the statuses of the pancreatic and pituitary glands.

In conclusion, we suggest an initial MEN1 gene mutation test be conducted in PHPT patients that have first-degree relatives with PHPT or hypercalcemia. Furthermore, in PHPT patients with a MEN1 gene mutation, we recommend thorough evaluations be conducted to eliminate the possibilities of pituitary, pancreatic, cricoid, and thymic carcinoid tumors.

REFERENCES

1. Adami S, Marcocci C, Gatti D. Epidemiology of primary hyperparathyroidism in Europe. *J Bone Miner Res* 2002;17 (Suppl 2):N18-23.
2. Mizusawa N, Uchino S, Iwata T, Tsuyuguchi M, Suzuki Y, Mizukoshi T, et al. Genetic analyses in patients with familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumour syndrome. *Clin Endocrinol (Oxf)* 2006;65:9-16.
3. Pannett AA, Kennedy AM, Turner JJ, Forbes SA, Cavaco BM, Bassett JH, et al. Multiple endocrine neoplasia type 1 (MEN1)

- germline mutations in familial isolated primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 2003;58:639-46.
4. Goudet P, Murat A, Cardot-Bauters C, Emy P, Baudin E, du Boullay Choplin H, et al. Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). *World J Surg* 2009;33:1197-207.
 5. Miedlich S, Lohmann T, Schneyer U, Lamesch P, Paschke R. Familial isolated primary hyperparathyroidism—a multiple endocrine neoplasia type 1 variant? *Eur J Endocrinol* 2001; 145:155-60.
 6. Nagamura Y, Yamazaki M, Shimazu S, Sano K, Tsukada T, Sakurai A. A novel splice site mutation of the MEN1 gene identified in a patient with primary hyperparathyroidism. *Endocr J* 2012;59:523-30.
 7. Tsuchida M, Yamato Y, Hashimoto T, Saito M, Hayashi J. Recurrent thymic carcinoid tumor in the pleural cavity. 2 cases of long-term survivors. *Jpn J Thorac Cardiovasc Surg* 2001; 49:666-8.
 8. Gibril F, Chen YJ, Schrupp DS, Vortmeyer A, Zhuang Z, Lubensky IA, et al. Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2003;88:1066-81.
 9. Teh BT, Zedenius J, Kytölä S, Skogseid B, Trotter J, Choplin H, et al. Thymic carcinoids in multiple endocrine neoplasia type 1. *Ann Surg* 1998;228:99-105.
 10. Marx SJ, Agarwal SK, Kester MB, Heppner C, Kim YS, Emmert-Buck MR, et al. Germline and somatic mutation of the gene for multiple endocrine neoplasia type 1 (MEN1). *J Intern Med* 1998;243:447-53.
 11. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature* 1988;332:85-7.
 12. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mutat* 2008; 29:22-32.
 13. Hannan FM, Nesbit MA, Christie PT, Fratter C, Dudley NE, Sadler GP, et al. Familial isolated primary hyperparathyroidism caused by mutations of the MEN1 gene. *Nat Clin Pract Endocrinol Metab* 2008;4:53-8.