



A Rare Combination: Multiple Endocrine Neoplasia Type 1 and Follicular Thyroid Carcinoma

Nadir Bir Kombinasyon: Multipl Endokrin Neoplazi Tip 1 ve Foliküler Tiroid Karsinomu

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Abstract

Multiple endocrine neoplasia Type 1 (MEN-1) is an inherited syndrome characterized by the development of endocrine tumors of the pancreas, parathyroid, and pituitary glands. Mesenchymal tumors and adrenal neoplasms might also accompany this syndrome. However, the syndrome is rarely associated with thyroid tumors in contrary to the multiple endocrine neoplasia Type 2 that includes medullary thyroid carcinoma. This case study presents a 44-year-old woman who was diagnosed with MEN-1 on the basis of her clinical characteristics, laboratory data, and the presence of endocrine tumors. Follicular thyroid carcinoma was detected in the patient when she was being operated for nodular goiter, 12 years ago. We report this rare case which is likely the third case in the available scientific literature.

Keywords: Multiple endocrine neoplasia Type 1; follicular thyroid carcinoma, nephrolithiasis; hypoglycemia; acromegaly

Özet

Multipl endokrin neoplazi Tip 1 (MEN-1) pankreas, paratiroid ve piüter bezlerde endokrin tümörlerin gelişimiyle karakterize, kalıtsal bir sendromdur. Mezenkimal tümörler ve adrenal neoplaziler de bu sendroma eşlik edebilir. Bununla birlikte, medüller tiroid karsinomu içeren multipl endokrin neoplazi Tip 2'nin aksine, bu sendrom, tiroid tümörleri ile nadiren ilişkilidir. Bu çalışmada, endokrin tümörlerin varlığı, laboratuvar verileri ve karakteristik klinik özelliklerin ışığında MEN-1 tanısı konan 44 yaşındaki bir kadın olgu sunulmaktadır. Olgu nodüler guatr için 12 yıl önce opere edildiğinde foliküler tiroid karsinomu tespit edilmişti. Mevcut bilimsel literatürde, muhtemelen 3. vaka olan bu ender olguyu bildirmekteyiz.

Anahtar kelimeler: Multipl endokrin neoplazi Tip 1; foliküler tiroid karsinomu; nefrolitiazis; hipoglisemi; akromegali

Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal-dominant hereditary syndrome associated with pituitary, parathyroid, and enteropancreatic endocrine tumors. Its estimated prevalence ranges from 1 in 10,000 to 100,000 (1). The syndrome arises from mutations of a putative tumor suppressor gene at chromosome 11q13 which encodes a 610-

amino acid protein, menin. Although the cellular and biochemical functions of menin are not well-known, loss of heterozygosity of the MEN1 locus appears in MEN1-related tumors (2). Patients with MEN-1 inherit an inactivated copy of MEN-1 in all cells; a second inactivation occurs postnatally in certain cells and neoplasia results from clonal expansion of the cells with dual inactivation (3).

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It has been reported that MEN-1 is associated with several mesenchymal neoplasms such as facial angiofibroma, skin collagenoma, cutaneous lipoma, and leiomyoma. Patients with MEN-1 less commonly may also present with tumors of other endocrine organs, including thyroid and adrenal glands. Notably, the coincidence of follicular thyroid carcinoma and MEN-1 is very rare. We found only two cases in the literature, the first being the Hurthle-cell thyroid carcinoma and the second being micro-invasive follicular thyroid carcinoma (4,5). Herein, we report a case with the coincidence of MEN-1 and follicular thyroid carcinoma and review the related literature.

Case Report

A 44-year-old female patient with acromegaly and follicular thyroid cancer was referred to our clinic for recurrent hypoglycemia. Hypoglycemic episodes were first detected in the urology clinic. Two months ago, this patient was hospitalized for percutaneous nephrolithotomy operation because of renal stone. The patient was 32 years old when she was diagnosed with acromegaly, and she had been operated for visual complaints due to pituitary macroadenoma. In the following four years, the patient is undergoing conventional radiotherapy and being treated with octreotide until now. She underwent thyroidectomy because of nodular goiter when diagnosed with acromegaly. The pathology of thyroidectomy was reported as follicular thyroid carcinoma. The patient received radioiodine therapy after the surgery, and she is taking levothyroxine, 125 mcg per day. Furthermore, she has a history of recurrent upper gastrointestinal bleeding.

On physical examination, she has an acromegalic face, enlarged hands and feet, a transverse incision scar on the neck, and two brownish skin lesions that were consistent with facial angiofibroma were detected in the nose (Figure 1). Laboratory tests revealed hyperinsulinemic hypoglycemia, elevated levels of gastrin and calcitonin, normocalcemic hyperparathyroidism, and hypogonadotropic hypogonadism. Additionally, the results of the oral glucose tolerance test revealed that the serum level of growth hormone (GH) was not suppressed (Table



Figure 1: Acromegalic face together with two brownish facial angiofibromas on the nose (informed consent was taken for the image from the patient).

Table 1. The laboratory findings of the patient.

| Test | Result | Reference Range |
|---------------------|-------------|-----------------|
| Fasting Glucose | 37 mg/dL | 70-100 |
| Fasting Insulin | 42 µIU/mL | 2.4-29.1 |
| Fasting Gastrin | 677 pg/mL | 25-125 |
| Calcium | 9.6 mg/dL | 8.4-10.2 |
| Parathyroid Hormone | 247 pg/mL | 12-65 |
| FSH | 1.5 mIU/mL | 23-116 |
| LH | 0.5 mIU/mL | 16-54 |
| Estradiol | <11 pg/mL | 0-40 |
| Prolactin | 26.4 ng/mL | 2.8-29.2 |
| GH* | 3.84 ng/mL | 0-2 |
| IGF-1 | 252 ng/mL | 101-267 |
| TSH | 0.01 µIU/mL | 0.4-4.5 |
| Free T3 | 2.45 pg/mL | 2.3-4.2 |
| Free T4 | 1.08 ng/dL | 0.89-1.72 |
| Basal Cortisol | 16.1 µg/dL | 4.6-22.8 |
| ACTH | 16.2 pg/mL | 7.2-63.3 |
| Calcitonin | 52.1 pg/mL | <0.5 ** |

ACTH: Adrenocorticotropic Hormone; FSH: Follicle Stimulating Hormone; GH*: Minimum Value of Growth Hormone after Orally Glucose Tolerance Test; IGF-1: Insulin-like Growth Factor-1; LH: Luteinizing Hormone; TSH: Thyroid Stimulating Hormone; ** in athyroidal individuals.

1). On conducting the abdominal computed tomography scan, we detected a 4 cm sized

calcified mass and a 6.5 cm sized solid mass on the body-tail junction of the pancreas and the left adrenal gland, respectively (Figure 2).

The overnight dexamethasone suppression test and the measurement of 24-hour urinary fractionated metanephrines and normetanephrines excluded subclinical Cushing's syndrome and pheochromocytoma, respectively. The patient had neither hypertension nor hypokalemia, which is why plasma renin activity and serum aldosterone concentration were not measured. Thereupon, the adrenal mass was considered non-functional. On conducting neck ultrasonography, a 1 cm sized hypoechoic nodular area consistent with parathyroid adenoma was found on the right inferior lobe of the thyroid. Moreover, the presence of parathyroid adenoma was confirmed by Technetium-99m-MIBI scintigraphy. On the dual-energy x-ray absorptiometry was detected osteoporosis. There was no residual tissue or recurrent mass of adenohypophysis on sellar magnetic resonance imaging. Based on these results, we considered that she had acromegaly, insulinoma, and primary hyperparathyroidism. As a result, the operation was recommended for the pancreatic and parathyroid tumors. Unfortunately, the patient insistently refused both operations despite our strong recommendations. On the other hand, the genetic analysis, which may contribute to the definitive diagnosis of MEN-1, could not be performed for technical reasons.

Discussion

Acromegaly is the pituitary component of MEN-1 in our patient. It is well-known that thyroid tumors can develop by the hyperstimulation of GH in patients with acromegaly. Therefore, the combination of MEN-1 and follicular thyroid carcinoma may not be surprising. Even though a few cases with the coexistence of MEN-1 and papillary thyroid carcinoma have been reported, the occurrence of follicular thyroid carcinoma with MEN-1 is rare (4,5). On the other hand, some of the recent classification systems suggest that follicular thyroid carcinoma should be assumed as a variant of papillary thyroid carcinoma rather than assigning it a distinct clinical entity. Nevertheless, all types

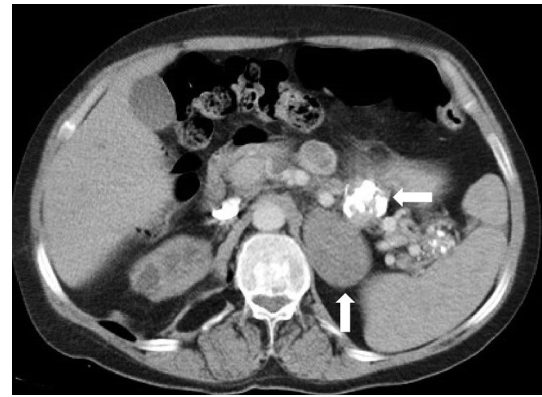


Figure 2: A calcified mass on the body-tail junction of the pancreas (horizontal white arrow) and a solid mass on the left adrenal gland (vertical white arrow).

of thyroid tumors are not included in the diagnostic criteria of MEN-1, unlike tumors of the pituitary, parathyroid, and pancreas. We aimed to emphasize that the tumor of the thyroid and/or adrenal glands are unusual in the patients with MEN-1.

Primary hyperparathyroidism (PHPT) is the most frequent and earliest manifestation of MEN-1; however, in our case, it was demonstrated 12 years after the diagnosis of acromegaly. The presence of nephrolithiasis and osteoporosis was also consistent with PHPT. Moreover, hypogonadism might have also contributed to the development of osteoporosis in the patient.

Enteropancreatic tumor component of the syndrome was probably insulinoma in our case even though gastrinomas account for the largest percentage of these tumors in MEN-1. Hyperinsulinemic hypoglycemia, together with a calcified solid mass on the pancreas, was documented. Also, fasting hypergastrinemia was detected in the patient. Hypercalcemia is a potent stimulus for gastrin secretion. Therefore, this can be a probable explanation for the occurrence of hypergastrinemia in a patient with PHPT; however, our patient was normocalcemic. Therewithal, the history of recurrent upper gastrointestinal bleeding led to the speculation of Zollinger-Ellison Syndrome, the eponym for the clinical syndrome, which is characterized by autonomous and excess gastrin production by a gastrinoma. Because of these conditions, we believe that the pancreatic mass secreted not only insulin but also gastrin. This could not be

proven as the patient refused the excision of pancreatic mass despite the fact that the clinical picture has suspected gastrinoma. Although some immunohistochemical studies have shown that the pancreatic endocrine tumors have the potential for multiple hormone production, the clinical manifestations are often related to hypersecretion of only one type of hormone. Several instances of sequential transition from one type of syndrome to another have been reported (6,7). Only one case in the literature has clearly demonstrated two clinically recognizable syndromes (Zollinger-Ellison Syndrome and insulinoma, concurrently), arising from a single pancreatic lesion, but this patient did not meet the criteria for MEN-1 (8).

Pituitary adenomas in MEN-1 may lead to headache and visual-field defects owing to tumor growth. Also, the production of excess hormones can cause various other symptoms. The majority of these lesions are reported to be prolactinomas. The first manifestation of the syndrome in our case was acromegaly; however, we did not find any residual or recurrent mass on sellar magnetic resonance imaging, although non-suppressible GH levels were detected. It might be explained by GH hypersecretion in the patients with MEN-1, which may occasionally be secondary to the ectopic secretion of growth hormone-releasing hormone. The other peptides that may rarely be over-secreted by pancreatoduodenal neuroendocrine tumors in MEN1 include parathyroid hormone-related peptide, adrenocorticotrophic hormone, somatostatin, and calcitonin. The serum levels of calcitonin which are expected to be too low to measure in an athyroidal individual were observed to be high in our case, even though she underwent total thyroidectomy. We assumed that calcitonin was hypersecreted from the pancreatic mass presumably because the patient had no residual thyroid tissue on neck ultrasonography. Cutaneous abnormalities such as angiofibromas, collagenomas, and lipomas are also common in MEN-1 patients. It has been shown that these lesions are also associated with the allelic loss of the MEN-1 gene, suggesting that they are benign neoplasms arising from clonal expansion. Facial angiofibromas were detected in

our patient with MEN-1. Over and above, we found an adrenal mass which may be considered as an uncommon component of MEN-1.

MEN-1 may also include uncommon neoplastic components such as adrenal and thyroid tumors. Since the role of menin as a tumor regulator in many organs remains to be established, it is difficult to distinguish between random observations and etiological relationships between MEN-1 cases and atypical tumors. Loss of heterozygosity of the MEN1 locus was examined in previous case series of MEN-1 patients with thyroid carcinoma (9,10); however, their results did not show any loss of heterozygosity and indicated no etiological relationship between the presence of MEN1 mutation and thyroid carcinoma. Therefore, these tumors appear to develop along pathogenetic pathways that are different from classical MEN-1-associated tumors. Nevertheless, further studies and additional case reports are required to clarify the possible mechanisms underlying the development of atypical tumors in MEN-1 patients.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ahmet Görgel; Design: Mustafa Demirpençe; Control/Supervision: Mitat Bahçeci; Data Collection and/or Processing: Sacit Nuri Görgel; Analysis and/or Interpretation: Sacit Nuri Görgel; Literature Review: Mustafa Demirpençe; Writing

the Article: Ahmet Görgel; Critical Review: Sacit Nuri Görgel; References and Findings: Mitat Bahçeci; Materials: Ahmet Görgel.

References

1. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debenlenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Roe BA, Weisemann J, Boguski MS, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL, Marx SJ. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997;276:404-407. [[Crossref](#)] [[PubMed](#)]
2. Guo SS, Sawicki MP. Molecular and genetic mechanisms of tumorigenesis in multiple endocrine neoplasia type-1. *Mol Endocrinol*. 2001;15:1653-1664. [[Crossref](#)] [[PubMed](#)]
3. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab*. 2001;86:5658-5671. [[Crossref](#)] [[PubMed](#)]
4. Kim YL, Jang YW, Kim JT, Sung SA, Lee TS, Lee WM, Kim HJ. A rare case of primary hyperparathyroidism associated with primary aldosteronism, Hürthle cell thyroid cancer and meningioma. *J Korean Med Sci*. 2012;27:560-564. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
5. Lodewijk L, Bongers PJ, Kist JW, Conemans EB, de Laat JM, Pieterman CR, van der Horst-Schrivers AN, Jorna C, Hermus AR, Dekkers OM, de Herder WW, Drent ML, Bisschop PH, Havekes B, Rinkes IH, Vriens MR, Valk GD. Thyroid incidentalomas in patients with multiple endocrine neoplasia type 1. *Eur J Endocrinol*. 2015;172:337-342. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
6. Liaw CC, Lin JT, Chen TJ. Multiple-hormone-producing islet cell carcinoma: report of a case. *Taiwan Yi Xue Hui Za Zhi*. 1989;88:722-725. [[PubMed](#)]
7. Thompson NW. Current concepts in the surgical management of multiple endocrine neoplasia type 1 pancreatic-duodenal disease. Results in the treatment of 40 patients with Zollinger-Ellison syndrome, hypoglycaemia or both. *J Intern Med*. 1998;243:495-500. [[Crossref](#)] [[PubMed](#)]
8. Lodish MB, Powell AC, Abu-Asab M, Cochran C, Lenz P, Libutti SK, Pingpank JF, Tsokos M, Gorden P. Insulinoma and gastrinoma syndromes from a single intrapancreatic neuroendocrine tumor. *J Clin Endocrinol Metab*. 2008;93:1123-1128. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
9. Vortmeyer AO, Lubensky IA, Skarulis M, Li G, Moon YW, Park WS, Weil R, Barlow C, Spiegel AM, Marx SJ, Zhuang Z. Multiple endocrine neoplasia type 1: atypical presentation, clinical course, and genetic analysis of multiple tumors. *Mod Pathol*. 1999;12:919-924. [[PubMed](#)]
10. Perakakis N, Flohr F, Kayser G, Thomusch O, Parsons L, Billmann F, von Dobschuetz E, Rondot S, Seufert J, Laubner K. Multiple endocrine neoplasia type 1 associated with a new germline Men1 mutation in a family with atypical tumor phenotype. *Hormones*. 2016;15:113-117. [[Crossref](#)] [[PubMed](#)]