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Case report

Lung adenocarcinoma and adrenocortical carcinoma in a patient with multiple endocrine neoplasia type 1

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ABSTRACT

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by heterozygous germline mutations in the tumor suppressor gene *MEN1*, which encodes a nuclear protein, menin. MEN1 is characterized by the combined occurrence of tumors involving the pituitary gland, pancreatic islets, and parathyroid glands. Additionally, patients with MEN1 often exhibit adrenal tumors. Although most MEN1-associated tumors are benign, malignant lesions arising in these endocrine organs have been reported. Additionally, malignant diseases of non-endocrine organs concomitant with MEN1 have also been reported. Here, we report a rare case of a MEN1 patient who exhibited adrenocortical carcinoma (ACC) and lung adenocarcinoma (LAC).

A 53-year-old Japanese woman was diagnosed with genetically proven MEN1 that initially manifested as parathyroid, pancreatic, and adrenal tumors. During the course of the disease, she developed LAC harboring the epidermal growth factor receptor gene mutations and cortisol-secreting ACC. Both tumors were surgically resected. The tumor cells were immunohistochemically negative for menin.

Studies have suggested a causative link between *MEN1* gene mutations and ACC, and menin expression may decrease in MEN1-related ACCs. In contrast, there are few reports suggesting a specific role of *MEN1* gene mutations in LAC. Menin is often inactivated in the LACs of patients without MEN1. Thus, our patient's ACC probably occurred as part of MEN1, whereas the latter had no evident etiological association with her LAC. This case demonstrates the need for physicians to consider the potential development of malignant diseases originating from both endocrine and non-endocrine organs in MEN1 patients.

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1; formerly known as Wermer syndrome) is a rare autosomal dominant disorder characterized by the combined occurrence of two or more tumors involving the parathyroid glands, pancreatic islets, and anterior pituitary gland, with or without overproduction of their organ-

Abbreviations: ACC, adrenocortical carcinoma; ALK, anaplastic lymphoma kinase; CT, computed tomography; EGFR, epidermal growth factor receptor; LAC, lung adenocarcinoma; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; SF-1, steroidogenic factor; TTF-1, thyroid transcription factor-1.

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specific hormones. MEN1 is caused by heterozygous germline loss-of-function mutations in the tumor suppressor gene *MEN1* located on chromosome 11q13, which comprises 10 exons and encodes a 610-amino acid protein, menin [1]. MEN1 tumors frequently have loss of heterozygosity of the *MEN1* locus. Patients with MEN1 also often exhibit central nervous system tumors, foregut carcinoids, cutaneous tumors, and adrenocortical tumors.

The majority of MEN1-associated tumors are benign, but malignant tumors arising in the pituitary, parathyroid, pancreatic islets, and adrenocortical glands have been reported [1,2]. Several cases of other endocrine or non-endocrine malignant diseases concomitant with MEN1, such as papillary thyroid carcinoma and ductal breast carcinoma, have also been reported [3,4]. However, MEN1 patients who exhibit primary lung cancer have not been described in the literature. Here, we present the case of a patient with MEN1 who exhibited both adrenocortical carcinoma (ACC) and primary lung adenocarcinoma (LAC).

2. Immunohistochemical analysis of menin expression in ACC and LAC

Menin expression in the resected ACC and LAC specimens (both tumor cells and adjacent non-tumoral tissues) was analyzed by immunohistochemistry using a monoclonal antibody against menin (Abcam Plc., Cambridge, UK).

3. Case presentation

A 52-year-old Japanese female presented with asymptomatic hypercalcemia at a routine medical check-up in 2001, and was diagnosed with primary hyperparathyroidism harboring parathyroid nodules. The patient underwent parathyroidectomy of the right lower parathyroid nodule and a microscopic examination indicated parathyroid adenoma. The patient still had mild hypercalcemia and was referred to our hospital in September 2002.

The patient had an unremarkable medical history and had taken no medications in her lifetime. She experienced menopause in her late 40s. Her family history revealed that her father had a cerebral infarction and her uncle had type 2 diabetes mellitus; none of her relatives had hypercalcemia or a lung or adrenal tumor. The patient had never smoked cigarettes or consumed alcohol. She was 157 cm tall and weighed 53 kg. Blood chemistry showed high serum calcium (10.8 mg/dL, reference range: 8.8–10.2 mg/dL), low to normal serum phosphorus (2.6 mg/dL, reference range: 2.5–4.5 mg/dL), and normal serum albumin levels (4.2 g/dL, reference range: 3.8–5.3 g/dL). Computed tomography (CT) showed 0.5- to 0.7-cm nodules in the left parathyroid glands, a 1.5-cm pancreatic tumor, a 1.0-cm right adrenal tumor, and a 2.0-cm left adrenal tumor (Fig. 1A and B). Basal serum levels of pancreatic and adrenal hormones, such as insulin, glucagon, gastrin, vasoactive intestinal peptide, aldosterone, and cortisol, were normal, but serum intact parathyroid hormone level (105 pg/mL, reference range: 10–65 pg/mL) was high. 99m-Tc-methoxyisobutylisonitrile scintigraphy revealed increased uptake in the left parathyroid nodule area. Brain magnetic resonance imaging (MRI) showed no abnormalities in the pituitary gland. An analysis of *MEN1* gene mutations identified a germline nonsense mutation (p.Gln209×) in exon 3. The patient was diagnosed with persistent primary hyperparathyroidism and pancreatic and bilateral adrenal tumors in association with MEN1. The *MEN1* gene analysis was also performed in one of her brothers (56 years of age) and yielded a negative result; none of the other relatives agreed to the analysis.

During the 7 years of follow-up, routine truncal CT was performed every 6 months. Almost no changes were observed in the size or function of her parathyroid, pancreatic, and right adrenal tumors; however, her left adrenal tumor gradually grew to more than 3 cm in size. It was recommended to the patient that she undergo surgery to treat her left adrenal tumor because of its possible malignancy, but she refused.

Routine CT performed in October 2010 showed a 1.5-cm tumor in the middle lobe (section 4) of her right lung (Fig. 1C). She presented with no respiratory symptoms such as cough and sputum. A transbronchoscopic lung biopsy revealed LAC. The patient underwent right partial lobectomy in December of the same year. The

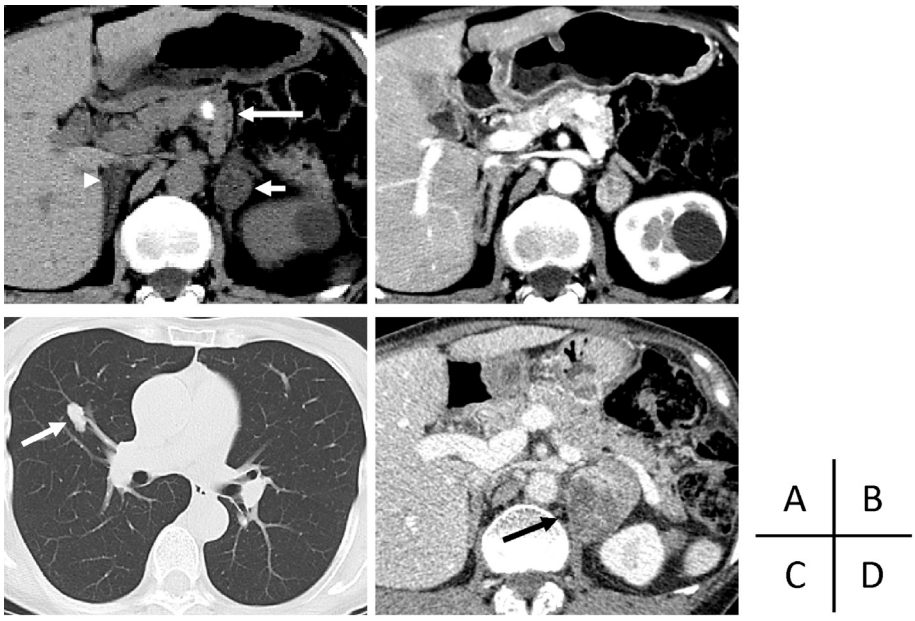

Fig. 1. Radiological findings. (A, B) Abdominal computed tomography (CT) (A, plain image; B, contrast-enhanced image) performed in October 2002 showing a 1.5-cm tumor with calcification in the pancreas (long arrow), a 1.0-cm tumor in the right adrenal gland (arrow head) and a 2.0-cm tumor in the left adrenal gland (short arrow). (C) Chest CT (plain image) performed in October 2010 showing a 1.5-cm tumor in segment 4 of the middle lobe of the right lung (arrow). (D) Abdominal CT (contrast-enhanced image) performed in April 2013 showing a 4.0-cm tumor in the left adrenal gland (arrow).

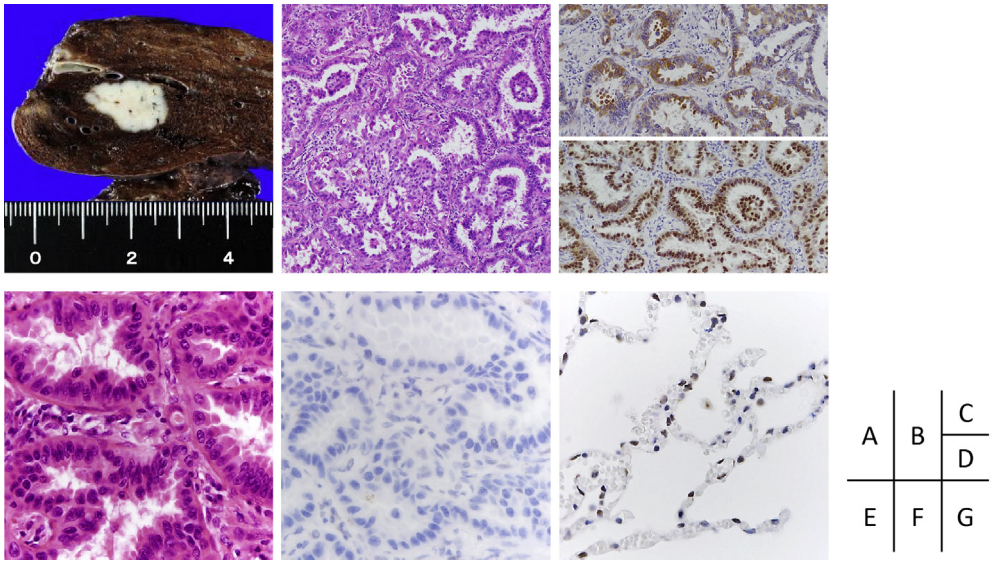

Fig. 2. Histological findings of the resected middle lobe of the right lung. (A) The gross appearance of the cut surface of the right lower lung shows a 1.8-cm tumor. (B–G) Proliferation of relatively well-differentiated atypical glands was observed (B, C; hematoxylin and eosin staining) indicating well-differentiated adenocarcinoma (acinar adenocarcinoma). The cytoplasm of the tumor cells was immunohistochemically positive for napsin A (D), and the tumor cell nuclei were positive for thyroid transcription factor-1 (E). Cell nuclei of the tumor cells were immunohistochemically negative for menin (F), whereas those of adjacent non-tumoral tissues were positive (G).

histopathological features were consistent with a well-differentiated adenocarcinoma (Fig. 2) [5]. Furthermore, they were immunohistochemically positive for napsin A and thyroid transcription factor-1 (TTF-1) and negative for cytokeratin5/6, p63, chromogranin A, steroidogenic factor 1 (SF-1), and neural cell adhesion molecule. Additionally, the tumor cells were immunohistochemically negative for both anaplastic lymphoma kinase (ALK) [6] and menin. A somatic mutation of the epidermal growth factor receptor (*EGFR*) gene was identified in exon 21 (p.Leu858Arg) [7]. Based on the staging system for lung cancer [8], the patient's LAC was classified as stage IA of IV (pT1aN0M0).

Truncal CT performed in April 2013 revealed no recurrent LAC and no changes in her parathyroid, pancreatic, and right adrenal tumors, with the exception of an enlarged left adrenal tumor (4 cm) (Fig. 1D). Although she did not present with a cushingoid appearance and had a normal basal serum cortisol level, her physiological cortisol circadian rhythm was disturbed. An iodine-131 adosterol scan showed uptake consistent with bilateral adrenal tumors with a left side predominance, indicating subclinical Cushing's syndrome [9] due to the left adrenal tumor.

Because the patient's left adrenal tumor became further enlarged, she finally agreed to adrenal surgery and underwent laparoscopic left adrenalectomy in March 2014. The tumor, which consisted mainly of clear cells and compact cells, exhibited coagulative necrosis, capsular invasion, nuclear atypia, and mitosis (Fig. 3); the Ki-67 labeling index was 8% in the hot spot. Weiss's criteria score [10] for her ACC was 6 out of a maximum score of 9. The tumor cells were immunohistochemically negative for napsin A

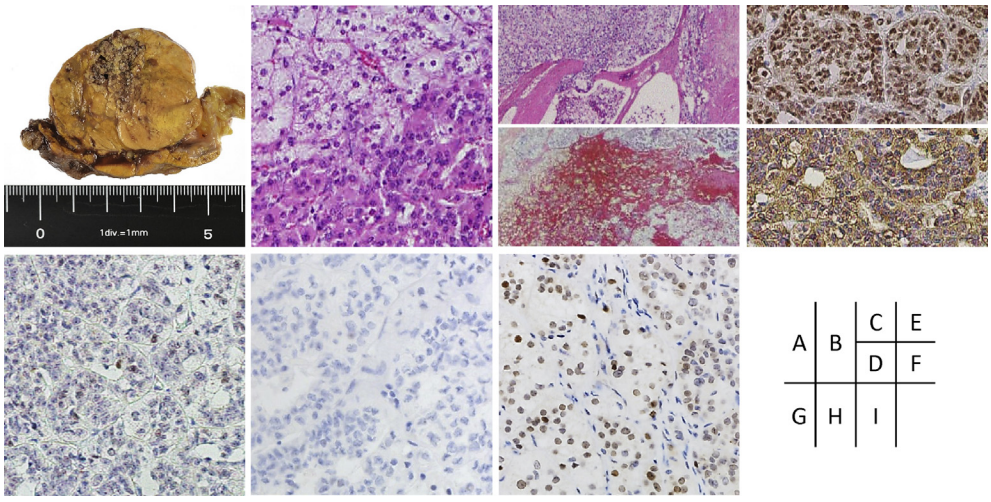

Fig. 3. Histological findings of the resected left adrenal gland. (A) The gross appearance of the cut surface of the left adrenal gland shows a 4.2-cm tumor. (B–I) The tumor consisted mainly of clear cells and compact cells (B; hematoxylin and eosin staining). The tumor contained a portion of coagulative necrosis and showed capsular invasion (C, D; hematoxylin and eosin staining). The immunostained nuclei of the tumor cells were positive for steroidogenic factor 1 (E), and the cytoplasm of the tumor cells showed positive immunostaining for 3β-hydroxysteroid dehydrogenase (F). Approximately 2% of the tumor cells were positive for p53 (G). Cell nuclei of the tumor cells were immunohistochemically negative for menin (H), whereas those of adjacent non-tumoral tissues were positive (I).

and TTF-1, but positive for SF-1 and steroidogenic enzymes, such as 3-beta-hydroxysteroid dehydrogenase and cytochrome P450c17. These findings were consistent with a cortisol-secreting ACC causing subclinical Cushing's syndrome [11]. The tumor harbored no aberrant expression of p53 [12]. The tumor cells were immunohistochemically negative for menin, while the adjacent non-tumoral tissues were positive for menin. Based on the staging classification [13], the patient's ACC was classified as stage I of IV (T1N0M0). The patient was informed of additional treatment options [14,15], including anticancer chemotherapy with mitotane and radiation therapy, to prevent or slow the development of local and distant recurrence of ACC. She did not consent to receive this form of additional treatment, after considering the potential benefits and side effects.

Two months after adrenal surgery, the patient had a normal physiological cortisol circadian rhythm, and an intravenous cosyntropin (0.25 mg) stimulation test showed normal cortisol release, indicating resolution of the subclinical Cushing's syndrome and normal functioning of the right adrenal gland.

The CT performed in September 2015 showed the appearance of tumors 1.1–1.4 cm in size in section 5 of the liver without local recurrence in the lung and adrenal glands. A liver biopsy revealed metastases from the ACC. The patient is being treated with anticancer drugs, including mitotane, for the distant recurrence of ACC.

4. Discussion

The present patient was diagnosed with genetically proven MEN1 in her early 50s; this condition initially manifested as parathyroid tumors associated with primary hyperparathyroidism, a pancreatic tumor, and adrenal tumors. During the clinical course of MEN1, the patient developed LAC and ACC, both of which were surgically resected. This is the first reported case of primary lung cancer associated with MEN1.

LAC is the most common histological form of primary lung cancer. Although most cases of LAC are associated with smoking, a role for genetic factors, including *EGFR* gene (chromosome 7p11.2) mutations and *ALK* gene (chromosome 2p23) rearrangements, in LAC has also been proposed [7]. However, few reports suggest a specific role for the *MEN1* gene mutation in LAC. On the other hand, several studies have shown that menin is often inactivated in the LAC of patients without MEN1 [16]. In the present case of a nonsmoker, an immunohistochemical examination did not identify abnormal ALK rearrangements or menin expression in LAC (Fig. 2F), and a gene analysis revealed *EGFR* mutations. These findings suggest that our patient probably developed EGFR-related LAC, and there was no evident etiological association between her LAC and MEN1.

ACC is a rare, aggressive tumor originating from the adrenal cortex, with an unclear pathogenesis and poor prognosis [15]. Even after complete resection in early-stage disease, recurrence is frequent. It has been suggested that genetic defects such as *P53* and *MEN1* gene mutations are involved in the development of ACC [17]. MEN1-related ACC sometimes occurs following small adrenal tumors [18]. Menin expression may be down-regulated in MEN1-related ACC [19], whereas the protein is highly expressed in cortisol-secreting ACC in patients without MEN1 [20]. In the present case, the absence of aberrant p53 expression, determined immunohistochemically, indicated that *P53* somatic mutations were unlikely [12]. The 2.0-cm left adrenal tumor detected at the time of the MEN1 diagnosis gradually grew to more than 4 cm in size over the following 10 years. Microscopic examination of the resected specimen revealed a cortisol-secreting ACC, in which no menin expression was detected by immunostaining (Fig. 3H). Therefore, our patient may have had MEN1-related ACC.

Pancreatic neuroendocrine tumors (islet cell tumors) occur in about half of MEN1 patients [1]. Many of these tumors secret excessive amounts of hormones such as insulin and gastrin, but some are nonsecretory. The radiologic features of nonsecretory pancreatic neuroendocrine tumors include calcification [21], as was the case in the pancreatic tumor of our patient (Fig. 1A and B). There were no clinical or hormonal manifestations, and its size and behavior remained unchanged during the subsequent >10-year clinical course of her MEN1. Therefore, our patient's pancreatic tumor was probably a benign, nonsecretory neuroendocrine tumor.

In conclusion, here we described the case of a patient with genetically proven MEN1 who developed ACC and LAC. The ACC probably occurred as part of her MEN1, but no etiological association could be established between her LAC and MEN1. The present case highlights the need to consider the potential development of malignant diseases originating from both endocrine and non-endocrine organs in patients with MEN1.

Conflicts of interest

The authors declare no competing interests.

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