NOTE

A novel case of myxoid variant of adrenocortical carcinoma in a patient with multiple endocrine neoplasia type 1

Ko Harada¹⁾, Miho Yasuda¹⁾, Kou Hasegawa¹⁾, Yuto Yamazaki²⁾, Hironobu Sasano²⁾ and Fumio Otsuka¹⁾

¹⁾ Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

²⁾ Department of Anatomic Pathology, Tohoku University Graduate School of Medicine, Miyagi 980-8575, Japan

Abstract. Adrenocortical carcinoma (ACC) is a rare malignancy arising from adrenocortical parenchymal cells. Myxoid ACC is one of the newly identified, rare, but important histological variants of ACC, characterized by the presence of abundant extracellular Alcian Blue-positive myxoid material. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant cancer predisposition syndrome, and the incidence of ACC in MEN1 patients has been reported to be between 1.4% and 6%. Here, we report the case of a 68-year-old Japanese woman harboring the past history of MEN1 associated with insulinoma, pituitary tumor, and hyperparathyroidism. She presented to our hospital with hypertension and hypokalemia. Imaging studies revealed a right adrenal tumor, and histological examination revealed myxoid ACC. Despite surgical resection of the tumor and mitotane therapy, the patient died 6 months after the surgery. To the best of our knowledge, this is the first reported case of the myxoid variant of ACC in a patient with MEN1. The patient's clinical course was characterized by the development of both multiple endocrine and non-endocrine neoplasm, hyperaldosteronism, and aggressive biological behavior. This case confirmed that myxoid morphology was also associated with aggressive behavior in ACC, but further studies are required to clarify the association between MEN1 and myxoid ACC.

Key words: Adrenocortical carcinoma, Multiple endocrine neoplasia type 1, Myxoid variant

ADRENOCORTICAL CARCINOMA (ACC) is a rare malignant neoplasm arising from adrenocortical parenchymal cells [1]. The incidence of ACC is approximately one to two per million population per year [2, 3]. It usually occurs in adults, with a peak incidence in the fifth decade of life, and women are more likely to be affected than men [4]. Patients with ACC generally have an unfavorable clinical outcome, and the average duration of overall survival has been reported 14.5 months, with a 5-year mortality rate of 75% to 90% [5, 6]. ACC has a

heterogenous morphology in its classical form and includes several rare histological variants, including oncocytic, myxoid, and sarcomatoid [7]. Among those subtypes, myxoid variant of ACC was recently identified and characterized by tumor cells arranged in cords, clusters, or pseudoglandular structures that are embedded in a prominent myxoid stromal background. Myxoid ACC is also considered to harbor more aggressive clinical course than non-myxoid ACC [8, 9].

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant cancer predisposition syndrome caused by mutations in the *MEN1* gene [10, 11]. Among these concurring pathology, adrenal involvement in MEN1 patients is relatively common but most of the lesions are hyperplasia and nonfunctioning [12]. Here, we report the rare case of a patient with MEN1 who developed myxoid ACC during the clinical follow-up.

Case Report

A 68-year-old Japanese woman with a history of MEN1 presented to our hospital with hypertension and hypokalemia. Her family history was significant in that

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Correspondence to: Ko Harada, M.D., Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
E-mail: me422084@s.okayama-u.ac.jp
Abbreviations: ACC, Adrenocortical carcinoma; MEN1, Multiple endocrine neoplasia type 1; CT, Computed tomography; SUV max, Maximum standardized uptake value; MRI, Magnetic resonance imaging; SF-1, Steroidogenic factor; 3 β HSD, 3 β -hydroxysteroid dehydrogenase; P450c17, 17 α -hydroxylase; CYP11B1, 11 β -hydroxylase; CYP11B2, Aldosterone synthase; DHEA-ST, Dehydroepiandrosterone sulfotransferase

her father had pituitary adenoma and pancreatic cancer, although neither her mother nor her children had any cancer or endocrine diseases. At the age of 38 years, she underwent surgery for resection of the insulinoma but a residual lesion was present in the tail of her pancreas, for which she had been administered diazoxide. At the age of 46, she received a right total mastectomy for breast cancer. At the age of 47, a nonfunctional pituitary tumor was detected and transsphenoidal surgery was performed. Subsequently, she underwent transsphenoidal surgeries for recurrent tumors at the ages of 56 and 59. At the age of 57, a parathyroidectomy was performed for primary hyperparathyroidism. At the age of 59, a thymectomy for a thymoma was performed. At the age of 67, she underwent a left partial mastectomy for left breast cancer. Based on this medical history, she was diagnosed with MEN1 associated with insulinoma, pituitary tumors, and hyperparathyroidism, even though *MEN1* gene analysis had not been performed.

As part of regular follow ups with our department, the patient received laboratory tests and imaging studies to check for disease recurrence. At the age of 68, she noticed hypertension and, therefore, visited our hospital. She had lost 10 kg of weight over the past year. On examination, her blood pressure was elevated to 173/112 mmHg. She did not have any features suggestive of Cushing's syndrome. Her laboratory data were summarized in Table 1. Her serum potassium level was extremely low, at 2.5 mmol/L. Her plasma aldosterone and serum cortisol levels were elevated to 694 pg/mL and 19.5 µg/dL, respectively, while basal ACTH level was low at 1.9 pg/mL. A low-dose dexamethasone (1 mg) suppression test revealed a serum cortisol level of 20.0 µg/dL. These laboratory data indicated the overproduction of aldosterone and cortisol. Fig. 1 shows the changes in laboratory data and right adrenal tumor over the last 3 years. Laboratory data on presentation showed high blood pressure, increased level of cortisol and aldosterone, and decreased level of potassium, adrenocorticotropin and plasma renin activity, compared to the values at last visit. Computed tomography (CT) showed gradual enlargement of the adrenal tumor over 3 years, which especially rapidly grew in the last 1 year. In X-1 year, we recommended her to receive further evaluation for the right adrenal tumor, but the patient refused it because of personal reasons. CT showed a right adrenal tumor measuring 70 mm in greatest diameter with 32 Hounsfield units (HU), and contrast-enhanced CT revealed a heterogeneously enhanced adrenal tumor (Fig. 2A–2B). Positron emission tomography/CT showed 18F-fludeoxyglucose uptake in the same region (standardized uptake value [SUV max]: 29.1) (Fig. 2C). Magnetic resonance imaging (MRI) chemical shift imaging revealed a

large irregular lesion that did not exhibit signal loss between in-phase and out-of-phase images (Fig. 2D–2E). On T2-weighted imaging, the tumor was found to be heterogeneous and hyperintense to the liver parenchyma (Fig. 2F).

Based on imaging findings and laboratory data, ACC was strongly suspected. At this point, no apparent metastasis to the other organs was detected. She underwent surgical resection of the right adrenal tumor and the right kidney, together with a part of the inferior vena cava. At the same time, a distal pancreatectomy was performed for the residual insulinoma. The adrenal tumor submitted for pathological examination consisted of a solitary dark-brown tumor with a thin fibrous capsule, and had a largest diameter measuring 70 mm (Fig. 3A). Microscopically, the tumor presented a total Weiss score of 7 out of 9 points, including high nuclear grade, high mitotic rate (24 mitoses per 10 high power fields), eosinophilic cytoplasm, diffuse architecture, venous invasion, sinusoidal invasion, and capsular invasion (Fig. 3B–3D). Alcian blue periodic acid–Schiff (AB-PAS) staining did reveal the presence of the myxoid material (Fig. 3E). Ki-67 labeling index was 21% in the hot spots (Fig. 3F). The tumor cells were immunohistochemically positive for steroidogenic factor 1 (SF-1) (Fig. 3G). In addition, 3β-hydroxysteroid dehydrogenase (3βHSD), 17α-hydroxylase (P450c17), 11β-hydroxylase (CYP11B1), aldosterone synthase (CYP11B2), and dehydroepiandrosterone sulfotransferase (DHEA-ST) (Fig. 3H–3L). Immunohistochemical study of adjacent normal adrenocortical tissue also revealed decreased expression of DHEA-ST, indicating the suppression of the hypothalamic-pituitary-adrenal axis due to overproduction of cortisol from the ACC.

Based on these pathological and immunohistochemical findings, we finally reached a diagnosis of a myxoid variant of ACC. The patient was started on mitotane therapy at 2 weeks after surgery. However, multiple metastases to her liver were detected at 14 weeks after surgery. The amount of mitotane used at this point was 70 g. The patient died at 24 weeks after the surgery because of hepatic and renal failures.

Discussion

The patient in our present study was diagnosed with MEN1 associated with insulinoma, pituitary tumor, and hyperparathyroidism. During the clinical course of MEN1, she developed ACC, which was surgically resected. To the best of our knowledge, this is the first reported case of a myxoid variant of ACC associated with MEN1.

MEN1 is an autosomal dominant hereditary syndrome.

Table 1 Laboratory data

Complete blood count		Biochemistry		Endocrine	
White blood cell	11,510 / μ L	Total protein	6.1 g/dL	Free thyroxine	1.49 ng/dL
Neutrophil	84.5%	Albumin	3.4 g/dL	Thyroid stimulating hormone	0.84 μ U/mL
Lymphocyte	8.3%	Total bilirubin	0.57 mg/dL	Luteinizing hormone	0.5 mIU/mL
Eosinophil	0.1%	Aspartate transaminase	36 U/L	Follicle stimulating hormone	5.5 mIU/mL
Red blood cell	424×10^4 / μ L	Alanine transaminase	58 U/L	Testosterone	13.9 ng/dL
Hemoglobin	13.6 g/dL	γ -glutamyl transpeptidase	96 U/L	Prolactin	41.5 ng/mL
Platelet	39×10^4 / μ L	Lactate dehydrogenase	498 U/L	Growth hormone	0.36 ng/mL
Tumor marker		Sodium	144 mmol/L	Insulin-like growth factor-1	121 ng/mL
Soluble interleukin-2 receptor	239 U/mL	Potassium	2.5 mmol/L	Adrenocorticotropin	1.9 pg/mL
Cytokeratin 19 fragment	3.4 ng/mL	Chloride	94 mmol/L	Cortisol	19.5 μ g/dL
Carcinoembryonic antigen	3.05 ng/mL	Corrected calcium	10.7 mg/dL	Plasma renin activity	0.8 ng/mL/h
Neuron specific enolase	24.3 ng/mL	Phosphate	2.9 mg/dL	Aldosterone	694 pg/mL
Carbohydrate antigen 19-9	28.7 U/mL	Intact parathyroid hormone	304 pg/mL	Dehydroepiandrosterone sulfate	67 μ g/dL
		Blood urea nitrogen	26.4 mg/dL	Urine free cortisol	247.8 μ g/day
		Creatinine	0.99 mg/dL	Urine aldosterone	58.8 μ g/day
		Fasting plasma glucose	112 mg/dL		
		Hemoglobin A1c	5.9%		

Abnormal data are shown in bold.

Fig. 1 Progression of tumor size and the related clinical features. Computed tomography (CT) shows gradual enlargement of the adrenal tumor over 3 years, with especially rapid growth in the last 1 year.

The most frequent features of MEN1 cases are primary hyperparathyroidism, pancreatic endocrine tumors, and pituitary adenomas. An involvement of the adrenal gland has been reported in between 20% and 40% of patients with MEN1. The incidence of ACC in patients with MEN1 has been reported as being between 1.4% and 6%

[12, 13]. The prevalence of ACC has been also reported approximately 10 times higher in patients who have adrenal tumors and MEN1 than in patients who have adrenal incidentalomas without MEN1 [13]. The genetic defects such as *p53* and *MEN1* mutations are related to the development of ACC [14].

Fig. 2 Imaging findings. Computed tomography (CT) shows a right adrenal tumor 70 mm in diameter (A, arrowhead), and contrast-enhanced CT reveals a heterogeneously enhanced adrenal tumor (B, arrowhead). Positron emission tomography/CT shows 18F-fluorodeoxyglucose uptake in the same region (standardized uptake value [SUV max]: 29.1) (C, arrowhead). On magnetic resonance imaging (MRI), chemical shift imaging shows a large irregular right-sided lesion that did not exhibit signal loss between in-phase (D, arrowhead) and out-of-phase (E, arrowhead) images. On T2-weighted imaging, the tumor was found to be heterogeneous and hyperintense to the liver parenchyma (F, arrowhead).

Fig. 3 Pathological findings. The adrenal tumor consists of a solitary dark-brown tumor with a thin fibrous capsule (A). Microscopically, the tumor presents a total Weiss score of 7 out of 9 points, including high nuclear grade, high mitotic rate, eosinophilic cytoplasm, diffuse architecture, venous invasion, sinusoidal invasion, and capsular invasion (B: $\times 100$, C: $\times 200$, hematoxylin and eosin staining, and D: $\times 100$, CD31 immunostaining). Alcian blue periodic acid–Schiff (AB-PAS) staining shows that the myxoid material is Alcian blue-positive (E). The Ki-67 labeling index is 21% in the hot spot (F). The tumor cells are immunohistochemically positive for steroidogenic factor 1 (SF-1) (G). In addition, they are positive for 3 β -hydroxysteroid dehydrogenase (3 β HSD) (H), 17 α -hydroxylase (P450c17) (I), 11 β -hydroxylase (CYP11B1) (J), aldosterone synthase (CYP11B2) (K), and dehydroepiandrosterone sulfotransferase (DHEA-ST) (L).

In the present case, the patient had a history of breast cancer and other MEN1-associated endocrine tumors. MEN1 is also related to the development of non-endocrine tumors, and female patients with MEN1 are reported to be at increased risk for breast cancer [15, 16]. In cases of MEN1, the mechanisms of tumor formation may involve the loss of menin function in a tumor precursor cell [10]. Several cases have been reported in which patients with MEN1 developed multiple endocrine and non-endocrine tumors. Jeong *et al.* reported a case of MEN1 accompanied by breast cancer, thymic tumor, adrenal cortical adenoma, thyroid carcinoma, uterine leiomyoma, and lung hamartoma [17]. The patient in their study had a germline *MEN1* gene mutation. In addition, Ohara *et al.* reported the case of a patient with MEN1 who developed both of adrenocortical carcinoma and lung adenocarcinoma [18]. In light of these previous cases and our own case, clinicians should be aware that both endocrine and non-endocrine tumors could possibly develop in patients with MEN1.

The myxoid variant of ACC was first reported in 1979 [19], and approximately 50 cases have been reported to date in the English-language literature to the best of our knowledge [9]. In the year 2017 World Health Organization classification, myxoid ACC was firstly recognized as the distinctive subtype of ACC [20]. Myxoid ACC is histologically characterized by the presence of abundant extracellular Alcian blue-positive myxoid material [21]. Tumor cells are generally arranged in cords, trabeculae, clusters, or pseudoglandular structures, often floating in pools or lakes of myxoid material [8]. These features could result in the difficulty of differential diagnosis, especially from metastatic adenocarcinoma to the adrenal gland [8, 20–22]. The majority of previously reported cases of myxoid ACC had clinical characteristics similar to those of conventional ACC, but Sung *et al.* indicated that the presence of myxoid histological features in ACC was indeed associated with more aggressive clinical behavior and poorer overall survival than conventional ACC [9], which may explain the relatively aggressive biological course of our patient.

Regarding the endocrinological features of ACC, approximately 60% of ACC patients present with an excess of adrenal steroid hormone, which most commonly manifests as Cushing's syndrome [2]. Aldosterone producing ACCs are relatively rare, accounting for approximately 13% of functioning ACCs, and manifest with hypertension with hypokalemia [23]. Our case was characterized by hypokalemia and hypertension on presentation, along with marked increases in plasma aldosterone and urine aldosterone, which was consistent

with hyperaldosteronism.

In MEN1 patients, clinical and biochemical screening is recommended every 6–12 months, while radiological screening of the pancreas, adrenal glands, and pituitary gland using MRI or CT should be performed every 12 to 36 months [24, 25]. Our patient was followed-up within this recommended interval; however, the adrenal tumor became extremely enlarged especially in the last year. Our case may suggest the necessity of more close, regular follow-ups in patients with MEN1 accompanied by adrenal tumor, including imaging studies of adrenal tumor or observation of laboratory data associated with hyperaldosteronism and hypercortisolemia, considering the rapid growth of ACCs.

On unenhanced CT, ACCs rarely have an attenuation value of less than 10 HU, and the specificity of this threshold for the identification of benign adenomas is approximately 98% [26]. In our case, attenuation values of the tumor were approximately 30 HU in the clinical course, which was consistent with an ACC. In addition, several case reports proposed that high signal intensity on T2-weighted imaging is one of the characteristics of myxoid adrenocortical tumors [27, 28], which was observed in our case. However, it is also a typical finding of other ACCs [26]; therefore, further reports are needed to determine imaging characteristics of myxoid ACCs.

In summary, we presented the first reported case of a myxoid variant of ACC in a patient with MEN1. The patient's clinical course was characterized by the development of multiple endocrine and non-endocrine tumors, as well as hyperaldosteronism. Despite surgery and mitotane therapy, the patient died of distant metastasis. The poor disease course and outcome detected in our present case are considered to be attributable to the presence of the myxoid histological variant. However, further studies are required to clarify the association between MEN1 and myxoid variants of ACC.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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