A rare case of oncocytic adrenocortical carcinoma clinically presented as an incidentaloma

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Abstract. Adrenocortical carcinoma (ACC) is a rare aggressive tumor originating from adrenocortical parenchymal cells and its incidence is approximately 1 per million population per year. An oncocytic ACC is a recently identified entity among the several known histopathological variants of ACC, which is characterized by oncocytic cells, and only a few cases in the available literature have reported this tumor. In contrast to conventional ACCs, oncocytic ACCs usually manifest as solitary lesions presenting in adults without any sex predilection. We report a case of a 70-year-old Japanese man who presented with an incidentally discovered retroperitoneal mass without any evidence of excessive corticosteroid secretion. Laboratory and imaging studies, as well as transgastric endoscopic ultrasound-guided fine needle aspiration failed to establish a definitive diagnosis. Thus, the patient underwent surgical resection of the left-sided peritoneal tumor. Weiss score was positive in 6/9 points and the tumor met two major criteria of the Lin-Weiss-Bisceglia (LWB) system leading to a diagnosis of an oncocytic variant of ACC. Based on our findings in this patient, we conclude that a combination of the Weiss and LWB criteria is required to determine the malignant potential of oncocytic adrenal tumors because ACCs and oncocytomas could be frequently indistinguishable. Careful histopathological examination is pivotal in confirming the oncocytic component in the lesion and hence definitive diagnosis of ACCs.

Key words: Adrenocortical carcinoma, Oncocytic variant, Oncocytoma

ADRENOCORTICAL CARCINOMA (ACC) is a rare aggressive tumor originating from adrenocortical parenchymal cells. The incidence of ACC is approximately 1 per million population per year and female is more frequently affected at any age \([1]\). Patients with ACC are usually associated with poor clinical outcome and its mean duration of overall survival was reported to be 14.5 months, with a 5-year mortality rate of 75\%–90\% \([2, 3]\). The classical ACC usually harbored heterogeneous histological features and may present with several further rare histopathological variants, including oncocytic, myxoid, and sarcomatoid subtypes \([4, 5]\). The oncocytic variant of ACC was recently identified among these subtypes and is histologically characterized by oncocytic cytoplasm in which abundant mitochondria was identified by immunohistochemistry and/or electron microscopy. Approximately 30–40 cases of oncocytic ACC have been reported in English literature \([6, 7]\). In contrast to conventional ACCs, oncocytic ACCs usually manifest as solitary lesions presenting in adults without any sex predilection \([8]\). We herein report a rare case of oncocytic ACC.

Case Report

A 70-year-old Japanese man presented with an incidentally discovered retroperitoneal mass. Abdominal ultrasonography performed during regular medical checkup revealed a mass (5 cm) located at the splenic hilum. He had a past medical history of hypertension, dyslipidemia, and paroxysmal atrial fibrillation, which
had been all well controlled with medication. He did not note any weight changes, loss of appetite, or fatigue prior to his visit. Physical examination revealed that his blood pressure was 142/92 mmHg and heart rate was 54 beats per min. His height, weight, and body mass index were 181.9 cm, 78.1 kg, and 23.6 kg/m², respectively. He did not have any features suggestive of Cushing’s syndrome. His laboratory data were summarized in Table 1. Serum cortisol, testosterone, and dehydroepiandrosterone sulfate (DHEAS), plasma aldosterone and catecholamine, as well as urinary free cortisol and aldosterone levels were within normal limits. However, the basal plasma ACTH level was low at 5.1 pg/mL (normal range 7.2–63.3 pg/mL). Plain computed tomography (CT) revealed a left-sided retroperitoneal tumor measuring 62 mm in greatest diameter, and contrast-enhanced CT revealed a heterogeneously enhancing tumor adjacent to the left adrenal gland (Fig. 1A–C). Chemical shift magnetic resonance imaging revealed a large irregular lesion that did not show signal difference between the in-phase and out-of-phase images, suggesting a lipid-poor tumor (Fig. 1D, E). T2-weighted imaging revealed that the tumor was heterogeneous and hyperintense to the liver parenchyma (Fig. 1F). ¹²³I-meta-iodobenzylguanidine (¹²³I-MIBG) scintigraphy revealed normal accumulation of the ¹²³I-MIBG in the bilateral adrenal glands, and ¹³¹I-Adosterol scintigraphy revealed no significant uptake by the left peritoneal tumor, suggesting a neoplastic lesion and/or a tumor originating from extra-adrenocortical tissue. Transgastric endoscopic ultrasound-guided fine needle aspiration of the retroperitoneal mass was performed, and cytological analysis of the specimen revealed a class III lesion, which are within the normal ranges. The patient was followed-up for 5 months after surgery without any recurrence. Subsequently, he underwent open surgery for resection of the left peritoneal tumor and left adrenal gland. Before surgery, it was not clear whether the tumor was benign or malignant, or from which tissue the retroperitoneal tumor had originated. Preoperative radiological imaging revealed the possibility of an un-differentiated tumor, such as adrenal gland cancer or retroperitoneal sarcoma, with invasion to the pancreatic body. Therefore, the surgical procedure was focused on obtaining a sufficient surgical margin, and a distal pancreatectomy, with extended dissection of the retroperitoneum, including the spleen, adrenal gland, and the crus adjacent to aorta, was performed. Cholecystectomy was concomitantly performed because of gallbladder sludge which could lead to cholecystitis in the postoperative phase. Histopathological examination of the retroperitoneal tumor adjacent to the left adrenal gland revealed a solitary tumor harboring a relatively thin fibrous capsule (Fig. 2A) without invasion of the surrounding organs. Macroscopically, the color on cut-section was brown/dark with necrosis, but there was no hemorrhage. Microscopically, the tumor cells contained abundant granular eosinophilic cytoplasm, and the Weiss score was 6 of 9 points including high mitotic rate, atypical mitoses, eosinophilic cytoplasm, coagulation necrosis, diffuse architecture and capsular invasion demonstrated by tumor cells (Fig. 2B, C). The Ki-67 labeling index was 14% at the hot spots (Fig. 2D). Immunohistochemical examination revealed tumor cells with immunopositivity for steroidogenic factor 1 and mitochondria (Fig. 2E, F). Tumor cells were also immunohistochemically negative for 11β-hydroxylase and aldosterone synthase and positive for 17α-hydroxylase and DHEA-sulfo transferase (DHEA-ST) (Fig. 2G–J). The adrenal cortex adjacent to the tumor demonstrated cortical atrophy of the zonae fasciculata and reticularis atrophy and reduced DHEA-ST expression (Fig. 2K, L).

Based on these histopathological and immunohistochemical findings, we diagnosed this case as an oncocytic variant of ACC. In addition, these results indicated that this tumor could have the capacity of producing biologically active corticosteroids including cortisol and the patient had been associated with chronic suppression of the hypothalamic-pituitary-adrenal (HPA) axis prior to surgery based on the findings in attached non-neoplastic adrenal gland. He was postoperatively administered with mitotane combined with replacement therapy using hydrocortisone because of rather high-grade nature of ACC. Serum cortisol, DHEAS, and plasma ACTH were 9.0 μg/dL, 16 μg/dL, and 61.8 pg/mL, respectively, which are within the normal ranges. The patient was followed-up for 5 months after surgery without any recurrence.

**Discussion**

Oncocytic ACCs constitute a rare histopathological variant of ACC. To the best of our knowledge, only a few cases have been reported in English literature but none in detailed histopathological evaluation including immunolocalization of steroidogenic enzymes. In 2017, the World Health Organization first recognized and classified the oncocytic variant as a distinctive subtype of ACCs [9]. Therefore, accurate histopathological diagnosis definitively warrants careful evaluation of the oncocytic component in tissue specimens. Macroscopically, oncocytic ACCs are usually large, rounded, encapsulated, brown-yellow well-circumscribed masses with a mean diameter of 8 cm (range 2–20 cm) surrounded by a thin rim of non-neoplastic adrenal tissue [10]. Microscopically, these tumors are generally characterized by diffuse proliferation of polygonal cells with abundant granular eosinophilic cytoplasm in which abundant...
Table 1

| Parameter                        | Value       |
|---------------------------------|-------------|
| White blood cell                | 5,480 /μL   |
| Neutrophil                      | 63.3 %      |
| Lymphocyte                      | 24.9 %      |
| Eosinophil                      | 4.2 %       |
| Red blood cell                  | 432 × 10⁶ /μL |
| Hemoglobin                      | 14.9 g/dL   |
| Platelet                        | 22 × 10⁹ /μL |

| Tumor marker                    | Value       |
|---------------------------------|-------------|
| Soluble interleukin-2 receptor  | 400 U/mL    |
| Cytokeratin 19 fragment         | 2 ng/mL     |
| Carcinoembryonic antigen        | 1.13 ng/mL  |
| Neuron specific enolase         | 12.9 ng/mL  |
| Carbohydrate antigen 19-9      | 4.5 U/mL    |

| Biochemistry                    | Value       |
|---------------------------------|-------------|
| Total protein                   | 6.8 g/dL    |
| Albumin                         | 4.3 g/dL    |
| Total bilirubin                 | 1.1 mg/dL   |
| Aspartate transaminase          | 18 U/L      |
| Alanine transaminase            | 12 U/L      |
| γ-glutamyl transpeptidase       | 21 U/L      |
| Lactate dehydrogenase           | 213 U/L     |
| Sodium                          | 143 mmol/L  |
| Potassium                       | 4.8 mmol/L  |
| Chloride                        | 108 mmol/L  |
| Corrected calcium               | 9.3 mg/dL   |
| Blood urea nitrogen             | 16.5 mg/dL  |
| Creatinine                      | 0.99 mg/dL  |
| Fasting plasma glucose          | 96 mg/dL    |
| Hemoglobin A1c                  | 5.6 %       |

| Endocrine                       | Value       |
|---------------------------------|-------------|
| Testosterone                     | 363.5 [242–972] ng/dL |
| Adrenocorticotropin             | 5.1 [7.2–63.3] pg/mL |
| Cortisol                         | 7.5 [3.8–18.4] μg/dL |
| Plasma renin activity           | 0.4 [0.2–2.7] ng/mL/h |
| Aldosterone                      | 6.8 [3.6–24.0] ng/dL |
| Dehydroepiandrosterone sulfate  | 157 [15–240] μg/dL |
| Adrenaline                       | 0.02 [0–0.1] ng/mL |
| Noradrenaline                    | 0.23 [0.1–0.5] ng/mL |
| Dopamine                         | 0.02 [0–0.03] ng/mL |
| Urine free cortisol              | 41.6 [26–187] μg/day |
| Urine aldosterone                | 1.2 [0–7.5] μg/day |

Mitochondria were identified by immunohistochemistry and/or electron microscopy, large nuclei with prominent nucleoli, occasional mononuclear and binucleated giant cells, extracapsular extension with vascular invasion and necrosis, and variable atypia with mitotic figures [6].

Accurate assessment of the malignant potential of adrenal cortical neoplasms is often challenging. Application of the Weiss criteria (Table 2) is the most widely used system to predict the biological behavior of conventional adenocortical tumors; occurrence of ≥3 of the 9 Weiss criteria distinguishes malignant from benign tumors [11]. In addition, the status of the Ki-67 protein expression, especially its labeling index, is significantly associated with tumor proliferation, and the Ki-67 labeling index is not only useful in distinguishing between benign and malignant adenocortical tumors but also in predicting postoperative clinical outcome of ACC patients. For instance, the European Network for the Study of Adrenal Tumors clinical guidelines recommend mitotane treatment in ACC patients who underwent radical surgery and harbored a high risk nature of the disease defined by Ki-67 labeling index of >10% [12]. In our patient, the total Weiss score was 6 of 9 points with Ki-67 labeling index of 14%, indicating a high-risk group of ACC and therefore, adjuvant mitotane therapy was administered to this patient.

Oncocytic ACCs has been known to represent a distinct subtype of adrenal neoplasms that differ from conventional ACCs with regard to clinical and prognostic features [8]. Previous reports showed that the prognosis of oncocytic ACCs may be more favorable than that of conventional ACCs [13, 14]. Both benign and malignant oncocytic adrenal neoplasms have diffuse architectures and high-grade nuclear features, which are markers of malignancy in the Weiss criteria. Therefore, it is suggested that the application of Weiss criteria alone to oncocytic ACCs can lead to misunderstanding of malignant potential. In 2004, Bisceglia et al. acknowledged the inaccuracy of the traditional Weiss criteria when applied to oncocytic ACCs and proposed the Lin-Weiss-Bisceglia (LWB) system (Table 3), for the classification of these neoplasms [14, 15]. The major criteria included in this LWB system included a mitotic rate of >5 mitoses/50 high-power field (HPF), any atypical mitoses, or venous invasion. The minor criteria include large-sized tumors (>10 cm and/or >200 g), necrosis, and capsular or sinusoidal invasion. Defining criteria include the cells with predominantly granular eosinophilic cytoplasm, and a high nuclear grade with a diffuse architectural pattern. According to the proposed working rules, the presence of any one of the major criteria indicated malignancy or oncocytic ACC, and the presence of 1–4 minor criteria indicates uncertain malignant potential.
Fig. 1 Imaging findings of oncocytic adrenocortical carcinoma
Plain CT scan showing a left adrenal tumor measuring 62 mm in diameter (A, arrowhead), and a contrast-enhanced CT scan showing a heterogeneously enhancing adrenal tumor on an axial view (B, arrowhead) and a coronal view (C, arrowhead). Image showing the normal left adrenal gland adjacent to the tumor (C, arrow). Chemical shift MRI showing a large irregular left-sided lesion without signal loss between the in-phase (D, arrowhead) and out-of-phase (E, arrowhead) images. T2-weighted imaging showing a heterogeneous and hyperintense tumor to the liver parenchyma (F, arrowhead).

CT, computed tomography; MRI; magnetic resonance imaging

Fig. 2 Histopathological findings of oncocytic adrenocortical carcinoma
Image demonstrating a solitary adrenal tumor with a thin fibrous capsule (A). Microscopic examination demonstrating tumor cells with abundant granular eosinophilic cytoplasm. The total Weiss score of the tumor was 6 of 9 points based on a high mitotic rate, atypical mitoses, eosinophilic cytoplasm, coagulation necrosis, diffuse architecture, and capsular invasion (B: ×40, C: ×100, hematoxylin and eosin staining). The Ki-67 labeling index is 14% at a hot spot (D). Immunohistochemical examination showing tumor cells immunopositive for (SF-1) (E) and mitochondria (F). Tumor cells showing negative expression of CYP11B1 (G) and CYP11B2 (H) but positive expression of P450c17 (I) and DHEA-ST (J). Adjacent adrenal cortex showing atrophic changes of the zona fasciculata and zona reticularis (K) and reduced DHEA-ST expression (L).

CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; DHEA-ST, dehydroepiandrosterone sulfotransferase; P450c17, 17α-hydroxylase; SF-1, steroidogenic factor 1
our present case, identification of 7 mitoses/50 HPFs and atypical mitoses definitively led to the diagnosis of oncocytic ACC. Renaudin et al. reported 43 patients with oncocytic adrenocortical tumors in France and showed that both the Weiss criteria and the LWB criteria seemed to overestimate the potential malignancy of these tumors [16]. Further studies would be necessary to characterize the malignant potential of oncocytic tumors more accurately.

In this case, we did not perform the suppression test for endogenous steroids because hypersecretion of adrenocortical hormones was not clinically detected prior to surgery. However, histological findings of the tumor and non-neoplastic adrenal gland in this particular case did indicate the presence of cortisol excess based on the cortical atrophy of the zonae fasciculata and reticularis in the adrenal cortex adjacent to the tumor along with reduced DHEA-ST expression in the zona reticularis, suggesting the chronic suppression of his HPA axis. Moreover, it is supported by the fact that plasma ACTH level recovered after the surgery. Approximately 60% of ACC patients are known as hormone-secreting tumors, and the steroid profiles often demonstrated disorganized steroidogenesis [17]. Compared to the characteristic oncocytic ACC, adrenal oncocytic neoplasms are usually nonfunctional tumors; only 17% of them are functional [13, 18]. Results of immunohistochemical findings of steroidogenic enzymes detected in our patient were also consistent with those previously reported in patients with ACC. That is, excessive cortisol secretion by an adrenal tumor could suppress his HPA axis leading to atrophy of the adjacent adrenal cortex. Therefore, evaluation of the adrenal gland adjacent to the tumor could provide inert information as to preoperative glucocorticoid secretion [19].

In summary, we report a rare case of an oncocytic ACC, treated with surgical resection and adjuvant mitotane therapy. Our case report highlighted that a combination of the Weiss and LWB criteria is required to accurately determine the malignant potential of oncocytic ACCs because these tumors are sometimes indistinguishable from oncocytomas. Histopathological diagnosis of ACCs requires careful evaluation to confirm the oncocytic component of the tumor. Close and careful evaluation of the adrenal gland adjacent to the tumor is also pivotal in confirming preoperative status of HPA of the patient and to select an appropriate postoperative treatment strategy. Moreover, it is essential to distinguish oncocytic ACC from classical ACC using histopathological and immunohistochemical findings.

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**Disclosure**

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

1. Volante M, Buttigliero C, Greco E, Berruti A, Papotti M (2008) Pathological and molecular features of adrenocortical carcinoma: an update. J Clin Pathol 61: 787–793.

2. Veytsman I, Niemen L, Fojo T (2009) Management of endocrine manifestations and the use of mitotane as a chemotherapeutic agent for adrenocortical carcinoma. J Clin Oncol 27: 4619–4629.

3. Balasubramaniam S, Fojo T (2010) Practical considerations in the evaluation and management of adrenocortical cancer. Semin Oncol 37: 619–626.

4. Duregon E, Cappellesso R, Maffeis V, Zaggia B, Ventura L., et al. (2017) Validation of the prognostic role of the “Helsinki Score” in 225 cases of adrenocortical carcinoma. Hum Pathol 62: 1–7.

5. Harada K, Yasuda M, Hasegawa K, Yamazaki Y, Sasano H, et al. (2019) A novel case of myxoid variant of adrenocortical carcinoma in a patient with multiple endocrine neoplasia type I. Endocr J 66: 739–744.

6. Panizzo V, Rubino B, Piozzi GN, Ubiali P, Morandi A, et al. (2018) Laparoscopic trans-abdominal right adrenalectomy for a large primitive adrenal oncocytoic carcinoma: a case report and review of literature. Am J Case Rep 19: 1096–1102.

7. Thway K, Olmos D, Shah C, Flora R, Shipley J, et al. (2012) Oncocytic adrenal cortical carcinosarcoma with pleomorphic rhabdomyosarcomatous metastases. Am J Surg Pathol 36: 470–477.

8. Kalra S, Manikandan R, Srinivas BH (2015) Oncocytic adrenal cortical carcinoma—a rare pathological variant. BMJ Case Rep 2015; pii: bcr2014208818.

9. Lloyd RV, Osamura RY, Klöppel G, Rosai J, Bosman FT, et al. (2017) WHO classification of tumours of endocrine organs. In: World Health Organization Classification of Tumours 10: 1–355.

10. Bolsios D, Blouhos K, Vasiliadis K, Asimaki A, Tsalis K, et al. (2007) Adrenocortical oncocyoma—a rare tumor of undefined malignant potential: report of a case. Surg Today 37: 612–617.

11. Weiss LM (1984) Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 8: 163–169.

12. Fassnacht M, Dekkers O, Else T, Baudin E, Berruti A, et al. (2018) European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the study of adrenal tumors. Eur J Endocrinol 179: G1–G46.

13. Wong DD, Spagnolo DV, Bisceglia M, Havlat M, McCallum D, et al. (2011) Oncocytic adrenocortical neoplasms—a clinicopathologic study of 13 new cases emphasizing the importance of their recognition. Hum Pathol 42: 524–533.

14. Mills JK, Khalil M, Pasieka J, Kong S, Xu Y, et al. (2019) Oncocytic subtypes of adrenal cortical carcinoma: aggressive in appearance yet more indolent in behavior? Surgery 166: 524–533.

15. Bisceglia M, Ludovico O, Di Mattia A, Ben-Dor D, Sandbank J, et al. (2004) Adrenocortical oncocyotic tumors: report of 10 cases and review of the literature. Int J Surg Pathol 12: 231–243.

16. Renaudin K, Smati S, Wargny M, Al Ghuzlan A, Aubert S, et al. (2018) Clinicopathological description of 43 oncocyotic adrenocortical tumors: importance of Ki-67 in histoprotostatic evaluation. Mod Pathol 31: 1708–1716.

17. Sasano H (1994) Localization of steroidogenic enzymes in adrenal cortex and its disorders. Endocr J 41: 471–482.

18. Mearini L, Del Sordo R, Costantini E, Nunzi E, Porena M (2013) Adrenal oncocyotic neoplasm: a systematic review. Urol Int 91: 125–133.

19. Sugawara A, Takeuchi K, Suzuki T, Itoi K, Sasano H, et al. (2003) A case of aldosterone-producing adrenocortical adenoma associated with a probable post-operative adrenal crisis: histopathological analyses of the adrenal gland. Hypertens Res 26: 663–668.