A case of adrenocortical adenoma harboring venous thrombus mimicking adrenal malignancy

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Abstract. Advances in imaging technology and its widespread use have increased the number of identified patients with bilateral adrenal incidentalomas. The pathology of bilateral adrenal incidentalomas is gradually elucidated by its increased frequency. Although there is no consensus regarding the optimal management of bilateral adrenal lesions, adrenal lesions that are suspected adrenocortical carcinoma on the basis of radiological imaging require surgical resection. We report a clinically interesting case of a 59-year-old female with adrenocortical adenoma harboring venous thrombus that mimicked adrenal malignancy. She was referred for evaluation of asymptomatic asymmetric lesions on both adrenal glands. Abdominal computed tomography and magnetic resonance imaging showed a 4.7-cm-diameter heterogenous lesion with peripheral enhancement in the right adrenal gland and a 2.0-cm-diameter homogenous lesion in the left adrenal gland. Adrenal scintigraphy with 131I-adosterol exhibited marked accumulation in the left lesion and slight accumulation in the middle inferior portion of the right lesion. Endocrine data revealed subclinical Cushing syndrome, and the patient underwent right laparoscopic adrenalectomy. The serum cortisol level was not suppressed on an overnight dexamethasone suppression test after the adrenalectomy. The resected tumor revealed a cortisol-producing adrenocortical adenoma harboring an organized and re-canalized venous thrombus, which was associated with focal papillary endothelial hyperplasia. This case illustrates the difficulty with preoperatively diagnosing this heterogeneously enhanced large benign adrenal lesion and differentiating it from adrenocortical carcinoma or angiosarcoma.

Key words: Adrenocortical adenoma, Organized venous thrombus, Subclinical Cushing’s syndrome

THE NUMBER of adrenal incidentalomas that are identified has increased due to advances in imaging and the widespread availability of imaging technology. Adrenal incidentalomas are commonly detected as unilateral lesions and the incidence of bilateral lesions is estimated to be 7.8% to 17% [1, 2]. The pathogenesis and clinical and biochemical characteristics of incidentally discovered bilateral lesions are reported to be distinct from those of unilateral adenomas [2-5]. Although there remains little consensus on the optimal management of incidentally discovered bilateral adrenal lesions, adrenal lesions that suggest adrenocortical malignancy on an imaging study require surgical resection.

We recently encountered a case of bilateral adrenal incidentalomas, one of which revealed an enlarged adenoma harboring a venous thrombus and presented with imaging characteristics that were indistinguishable from adrenal adrenocortical carcinoma or angiosarcoma. Clinical and radiographical features of this rarely reported adrenal lesion have been described and the literature was reviewed.

Case Report

A 59-year-old woman with a 5-year history of dyslipidemia was referred for evaluation of asymptomatic bilateral adrenal lesions that were incidentally identified on a computed tomography (CT) scan. Her body weight was 54 kg and height was 157 cm. On physical examination, she was afebrile with a pulse of 56 beats per minute and normotensive at 110/60 mmHg without any signs or symptoms suggesting Cushing’s syndrome. Routine laboratory examinations showed normal complete blood cell counts, blood coagulation tests, and serum chemistry results including liver enzyme levels, renal function, ...
lipid profile, and calcium metabolism. Fasting glucose and glycosylated hemoglobin (HbA1c) were 5.0 mmol/L and 5.6%, respectively. Endocrine data (Table 1) showed that fasting plasma adrenocorticotropic hormone (ACTH) and serum cortisol levels were 3.3 pg/mL and 6.66 μg/dL, respectively. The circadian rhythms for ACTH and cortisol levels were disrupted. The serum cortisol levels were not suppressed after overnight 1-mg and 8-mg dexamethasone suppression tests (2.24 μg/dL and 2.93 μg/dL, respectively). Twenty-four-hour urinary free cortisol was within the normal limits (70.9 μg/day, normal range from 11.2 to 80.3 μg/day). These data supported a diagnosis of subclinical Cushing’s syndrome (SCS). Contrast-enhanced CT scan of the adrenal glands revealed bilateral adrenal tumors (Fig. 1). The right adrenal lesion was 4.7 cm in diameter with peripheral enhancement, while the left lesion was 2.0 cm in diameter with homogenous enhancement. On magnetic resonance imaging (MRI), the left adrenal lesion exhibited a slightly low signal intensity on T1-weighted imaging and very low signal intensity on T2-weighted imaging (Fig. 2A, 2B). There was a significant decrease in the signal intensity on out-of-phase in T1-weighted imaging (Fig. 2C). The right adrenal tumor exhibited low signal intensity on the periphery with slightly high signal intensity at the center on T1-weighted imaging (Fig. 2A). T2-weighted imaging in the right lesion showed three components, which were low signal intensity, high signal intensity, and very low signal intensity from the outside of lesion (Fig. 2B). There was a significant decrease in the signal intensity on the periphery only on out-of-phase in T1-weighted imaging (Fig. 2C). Gadolinium-enhanced images showed the right adrenal lesion with peripheral enhancement in the early phase and heterogenous enhancement in the delayed phase (Fig. 2D). Adrenal scintigraphy with 131I-adosterol (Fig. 3, posterior view) exhibited marked accumulation in the left lesion and slight accumulation in the middle inferior portion of the right lesion. On the basis of the radiological findings, the left adrenal lesion was diagnosed as a typical adrenal adenoma, but the definitive diagnosis of the right adrenal lesion was limited because of the non-specific radiological findings, which included atypical adenoma, carcinoma, hemangioma, or angiosarcoma as a differential diagnosis.

Because of the large size and heterogenous enhancement of the right lesion, which suggested an adrenal malignancy, the patient underwent laparoscopic right adrenalectomy. The patient received hydrocortisone replacement therapy (5 mg/day) for 3 months after the

| Table 1  | Laboratory characteristics of the endocrine profiles at the preoperative | Reference Values |
|----------|-------------------------------------------------|------------------|
| ACTH (pg/mL) | 3.3 | 7.2–63.3 |
| Cortisol (μg/dL) | 6.66 | 7.07–19.60 |
| Dehydroepiandrosterone sulfate (μg/dL) | 13 | 8–188 |
| Plasma renin activity (ng/mL/hr) | 0.3 | 0.3–2.9 |
| Aldosterone (pg/mL) | 50.9 | 35.7–240 |
| Testosterone (ng/mL) | 0.03> | 0.11–0.47 |
| Urinary cortisol (μg/24 h) | 70.9 | 11.2–80.3 |
| Morning | | |
| Midnight | | |
| ACTH (pg/mL) | 3.3 | 3.9 |
| Cortisol (μg/dL) | 6.66 | 4.28 |
| 1 mg DST | 2.24 | 2.93 |
| 8 mg DST | | |
surgery. The serum cortisol level was not suppressed after an overnight oral 1-mg dexamethasone suppression test 6 months after the adrenalectomy (2.38 μg/dL).

The resected adrenal lesion was composed of a 4.0 × 4.0 × 2.8-cm-sized solid mass appearing yellow to brown on the surface, which was partially encapsulated and attached to the residual adrenal gland (Fig. 4A). The lesion also had multiple components on the cut surface.
The central portion of the resected tumor was composed of a large venous thrombus that was partially organized and re-canalized, and it was also surrounded by a well-circumscribed adrenocortical tumor, which was composed of clear cells. Based on the Weiss criteria, the tumor was histopathologically diagnosed as adrenocortical adenoma [Score of Weiss criteria: 0] (Fig. 5A, 5B) [6]. At the adjacent portion to the thrombus, a dilated adrenal vein with hyalinized vascular wall was identified with hyalinized adrenal cortical cells, and CD31-positive focal papillary endothelial hyperplasia (PEH) (Fig. 5A, 5B, 5M, 5N). These histological findings were considered to be due to disrupted circulation in the region. Adrenocortical tumor cells were positive for 3β-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase (P450c17), and 11β-hydroxylase (CYP11B1) (Fig. 5C–H) and negative for dehydroepiandrosterone-sulfotransferase (DHEA-ST) and aldosterone synthase (CYP11B2) (Fig. 5I–L), which was histologically consistent with the finding of cortisol-producing adenoma. DHEA-ST immunoreactivity in the adjacent zona reticularis was suppressed, suggesting that cortisol production from this adenoma could suppress the status of the hypothalamic-pituitary-adrenal axis over a long period of time in patients with this disease.

**Discussion**

SCS is associated more frequently with bilateral lesions than with a unilateral lesion [2, 7-9]. Our case fulfilled the clinical diagnostic criteria for SCS [10] and showed immunohistologically negative DHEA-ST expression in the zona reticularis of the resected residual normal adrenal gland tissue, indicating cortisol production from this adenoma (Fig. 5F). Adrenal scintigraphy with 131I-adosterone that was performed pre-operatively revealed bilateral functional adrenal tumors (Fig. 3).

In bilateral adrenal lesions with ACTH-independent CS, a size difference between left and right tumors has not been clearly documented in the literature [11]. In our patient, the right and left adrenal lesions showed distinct features on CT and MRI. The left adrenal lesion was a typical lipid-rich adenoma with a well-circumscribed homogenous ovoid mass without calcification or necrosis, a density of less than 10 Hounsfield units (HU) on non-contrast enhanced CT, hypo-intensity on T2-weighted image, a high signal on in-phase imaging, and a decreased signal in the out-of-phase images on MRI [12, 13]. Conversely, the morphological features of the patient’s right adrenal lesion were indicative of adrenocortical malignancy on CT scan, which included a tumor size that was greater than 4 to 6 cm, an irregular margin with heterogeneity, an attenuation coefficient of 10 HU at unenhanced CT, and/or the necrosis, cyst and hemorrhage formation particularly in the central part of the lesion [14, 15]. The high intensity on a T1-weighted
image and low intensity on T2-weighted image that was observed in the central part of the right adrenal lesion suggested an effect of methemoglobin, which indicates the presence of blood components (Fig. 2B). The peripheral part of the right adrenal lesion surrounding the central hemorrhage formation was enhanced and comprised...
of the following two components: the outer layer had low intensity and the inner layer had a high intensity on T2-weighted imaging, although they were indistinguishable on T1-weighted imaging (Fig. 2B). The outer layer showed a significant decrease in the signal intensity on out-of-phase T1-weighted imaging (Fig. 2C), while both layers showed rapid and prolonged enhancement on gadolinium-enhanced MRI (Fig. 2D). Adrenal lesions showing prolonged peripheral enhancement on CT or MRI may be either a hemangioma or an angiosarcoma, both of which are rare. However, in our case, the peripheral enhanced component showed accumulation of $^{131}$I-adrenosterol on adrenal scintigraphy, which is suggestive of adrenocortical tissue (Fig. 3). Most adenomas are thought to show rapid enhancement on the arterial phase and early washout on the venous phase, while most malignant lesions show poor enhancement on the arterial phase and heterogenous or peripheral enhancement on the venous phase [16, 17]. Another study reported that the difference of peak gadolinium-enhancement between adenomas and malignant lesions was only 25 sec [18]. Moreover, there are atypical adrenocortical adenomas with malignancy-like findings, such as calcification, hemorrhage and cyst changes, or mixed lipid-rich and lipid-poor parts on CT or MRI imaging [19] and combined cases of angiosarcoma with adrenal cortical adenoma [20, 21]. The results of the literature review indicate the complexity and difficulty of making an accurate diagnosis from such imaging findings in the adrenal lesion.

The optimal treatment for patients with bilateral cortisol-secreting adenomas remains uncertain. The previous study suggested that the bilateral adrenalectomy may be indicated if urinary cortisol levels were higher than 3–4 times the upper limit of normal with both adrenals having a relatively symmetrical size [22]. Our case did not fulfill this criteria. Because the bilateral adrenalectomy requires life-long adrenocortical replacement, preservation of the maximum normal adrenal gland is strongly recommended even if the resection of bilateral lesions is mandatory [23]. When considering the unilateral adrenalectomy in the unilateral adrenal lesions with similar characteristics on both sides, adrenal vein sampling was an informative method to confirm the lateralization of cortisol hypersecretion [24].

In the present case, the cause of the distinct laterality of the bilateral benign tumors was evident from the histopathology. The gross pathological findings revealed that the adrenocortical adenoma had an organized and recanalized thrombus (Fig. 4B), and histopathological findings surrounding the large thrombus including CD31-positive focal PEH indicated the sequence of vascular events that had followed venous insufficiency (Fig. 5B). PEH is generally considered to be a benign proliferation of endothelial cells with secondary thrombosis and fibrin deposition or an excessive reaction to a normal reorganization process in the thrombus [25]. Although the exact pathological features that result from right adrenal lesion vascular insufficiency compared with that of the left lesion remain uninvestigated, PEH was reported to be present in 27% of the adenoma cases that are associated with hemorrhage, but there was no description of laterality [26]. In the present case, the lateralized asymmetry of adrenal adenomas can be speculated to have resulted from the anatomical localization of the adrenal glands. The right adrenal gland is surrounded by the liver and kidney [27], and it has a shorter right adrenal vein compared with the left adrenal vein. Therefore, if there is adrenal tumor enlargement, significant vascular insufficiency such as blood congestion or hemorrhage may be more likely to develop in the right adrenal lesion, ultimately leading to the development of organized venous thrombus, re-canalized thrombus, and associated PEH, which were indistinguishable from adrenal malignancy in the imaging study. The prolonged periphery enhancement in the lesion was thought to reflect the histological feature of blood filled vascular insufficiency (Fig. 2D). This finding was especially difficult to distinguish from angiosarcoma. Angiosarcoma is a rare malignant neoplasm that stains positive for CD31, but it can be distinguished from PEH by the histological confinement within the vascular lumen without frank tumor necrosis, marked pleomorphism, and/or a high mitotic index.

In summary, we report the case of a patient with bilateral functioning adrenocortical adenoma causing SCS who underwent unilateral laparoscopic adrenalectomy to resect an enlarged right lesion that presented with CT and MRI features that are characteristic of adrenal malignancy. We compared the pathological results and imaging data of this rarely reported cortisol-producing adrenocortical adenoma that harbored a large venous thrombus. Our case adds information about heterogeneously enhanced large adrenal lesion pathology, which should be considered in the differential diagnosis of adrenocortical carcinoma and angiosarcoma.

**Disclosure Statement**

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

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