Double unilateral functioning adrenocortical adenomas

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Abstract
Double functioning adrenocortical adenomas, occurring in the same gland is an extremely rare condition. This paper presents two cases of double functioning adrenocortical adenomas within the same adrenal gland, causing primary aldosteronism. Diagnosis was set histopathologically in one case since magnetic resonance imaging (MRI) failed to distinguish the two entities. In each case, a laparoscopic adrenalectomy was conducted. When preoperative imaging studies fail to report the presence of double adrenocortical adenomas, histopathology reports should be comprehensive enough so as to reveal such rare lesions.

Keywords: adrenocortical adenomas, primary aldosteronism, laparoscopic adrenalectomy, hypertension, hypokalemia.

Introduction
A form of secondary hypertension found in many patients is caused by autonomous adrenal aldosterone production, being referred to as primary aldosteronism (PA). According to some studies, PA is responsible for 5–20% of cases of secondary hypertension [1–4]. This high variability may be due to differences in the selection of patients with hypertension and the variability of diagnostic procedures in different regions of the world [5].

Although most often PA is clinically characterized by hypertension and hypokalemia, numerous studies have shown that PA causes multiple cardiovascular complications, sometimes independent of blood pressure (rhythm and conduction disorders), heart failure, myocardial infarction [6–9], cerebrovascular disease [10], and even kidney failure [11, 12]. As such, PA is a condition that negatively affects the quality of life [13].

There are two main causes involved in the etiopathogenesis of PA: bilateral suprarenal hyperplasia and adrenal adenomas of functional adrenal glands. The two entities account for about 90% of PA cases [14]. Other causes are aldosterone-producing adrenal carcinoma, unilateral adrenal hyperplasia, or familial hyperaldosteronism [12]. As for aldosterone-producing adenomas (APAs), these are benign, single, unilateral tumors of about 1 cm to 3 cm in diameter, coming from glomerular adrenal gland cells of the adrenal gland [15]. They are responsible for 30–40% of PA cases [16].

Case presentations

Case No. 1
The first patient, 46-year-old female, presented in the Emergency Room complaining of heart palpitations and severe headache. She had a 6-year history of hypertension under medication but with inadequate blood pressure control. The initial laboratory studies showed hypokalemia (2.7 mmol/L). The patient was administered oral potassium and Spironolactone. The re-evaluation showed insufficient regulation of arterial hypertension and persistent hypokalemia and was referred to the Department of Endocrinology. Further laboratory investigation was conducted and revealed a serum aldosterone level of 474 pg/mL and plasma renin activity (PRA) of 0.08 ng/mL/h. An abdominal computed tomography (CT) scan was performed and confirmed the presence of a nodule measuring 1.7 cm in the right adrenal gland. She was referred to the Department of Surgery, where she underwent a laparoscopic adrenal excision in the lateral decubitus position.

The macroscopic examination of the resection piece revealed an enlarged, irregular adrenal gland, having two yellow ovoid cell masses of approximately 0.5 cm and 1.4 cm in diameter, respectively. For the microscopic study, the resection piece was fixed in 10% neutral formalin solution and included in histological paraffin. The 3 μm to 4 μm sections of the microtome were stained with Hematoxylin–Eosin (HE) and examined under microscope.

Microscopically, the two structures had same characteristics of two adenomas from adrenal cortex. They were made up of polyhedral-like cells with clear, abundant cytoplasm, with small and hypochrome nuclei, organized in islands, acins or cords, separated by fine connective tissue.
septa. Very rarely, cells were seen in mitosis. The tumoral stroma was represented by fine connective septae detached from the glandular capsule, made up of collagen fibers and rare fibroblasts. The vascular network was poorly represented. Tumor formation did not invade the adrenal gland capsule (Figure 1).

Case No. 2

The second patient was a 56-year-old woman. Over the course of the last year, she was diagnosed with hypertension and was under endocrinological control. She was on Spironolactone 50 mg once daily. The medical history of the patient included a total abdominal hysterectomy. Laboratory evaluation indicated serum aldosterone levels of 711 pg/mL and abdominal CT scan showed a hypodense mass in the left adrenal gland, measuring 2.5 cm. After further evaluation of the preoperative CT scan, a reconstructed contrast-enhanced image revealed the second mass which was found (Figure 2). Because of hypertension control failure and persistent hypokalemia, surgical operation was suggested. Laparoscopic adrenalectomy was performed. Histological examination revealed two adrenocortical adenomas, 2 cm and 1.5 cm in diameter, respectively, yellowish, well defined, spaced apart in the glandular parenchyma (Figures 3). The microscopic examination performed on preparations fixed in 10% formalin and included in paraffin showed the presence of benign tumor cells in curves, acins or cords, with clear cytoplasm similar to cells in the fasciculated area of the adrenal gland, and also small cells with eosinophil cytoplasm and round hyperchromic nucleus, similar to cells in the reticulated adrenal region. Also, in this case, the tumor stroma was poorly represented (Figure 4).

Discussions

PA is the most common cause of secondary endocrine hypertension [8]. This form of hypertension may have a severe progression and the affected patients have an increased risk of cardio-cerebrovascular complications compared to the same age and gender patients who have essential hypertension [9, 17].

One of the major etiological causes of PA is the functional adrenal adenoma of the adrenal gland (aldosterone producer). Studies claim that most of the adenomas are inoperable, being accidentally discovered on abdominal imaging [CT or magnetic resonance imaging (MRI)] investigations performed for other conditions [18, 19].

Figure 1 – Microscopic aspects of the tumor: (A) Image of an area of the right adrenocortical gland, in which the adenoma that occupies the largest part of the area of the gland, which tends to delineate the rest of the gland, is observed – on the left side of the image is an area in which the gland appears normal; (B) Detail of the adenoma consisting of polyhedral cells with clear cytoplasm, vacuolar nucleus and central nuclei, rounded or oval, with central mitoses, similar to cells in the fasciculated area of the gland; (C) Microscopic image of the stroma; (D) Tumor cells organized in islands or nests that do not invade the glandular capsule. HE staining: (A) ×40; (C) ×100; (B and D) ×200.
Adrenal adenomas occur most often as single, unilateral tumor formations smaller than 3 cm [20]. When several nodular formations with dimensions less than 1 cm are identified, consideration should be given to the presence of a bilateral nodular hyperplasia [17, 21], which produces aldosterone and hypertension, but benefits from a medicinal treatment.

We have presented here two cases of unilateral duplicate adenomas, with aldosterone secretion (functional adenomas) in two patients with high blood pressure and hypokalemia, resistant to drug treatment. Laboratory investigations have shown elevated serum aldosterone levels, hypokalemia and altered aldosterone/renin modulation, paraclinic data suggesting the existence of a bilateral tumor or bilateral
hyperplasia of adrenal cortex. The clinical picture of the disease suggested that these were cases of PA. We considered such a possibility because some studies have shown that PA is quite common, affecting between 5% and 20% of patients with hypertension [22–24]. Currently, even in the absence of hypokalemia, aldosterone plasma levels increase in arterial hypertension patients and alteration of aldosterone and plasma renin activity are essential elements in PA diagnosis [25–27].

To obtain additional data on PA etiopathogenesis, we performed CT scans in both cases that revealed the presence of tumoral masses in the right and left adrenal glands, respectively. Currently, CT examination of the adrenal glands in clinical PA cases brings important data in establishing the positive and differential diagnosis, but also in establishing the therapeutic response, because adrenal adenomas can be surgically treated, while bilateral idiopathic adrenal hyperplasia requires medical treatment [28–31].

The final diagnosis of adrenal adenomas belongs to the histopathological examination. In our case, the macroscopic examination of the surgically resected pieces revealed the presence of two nodular formations (adenoids) in each case in the same gland, separated by normal glandular tissue. To our knowledge, this is the second paper that presents this entity [32].

The microscopic examination showed that adenomas were formed predominantly from large, polyhedral cells with clear, vacuolar cytoplasm, and round nuclei or centrally located ovals, similar to cells in the zona fasciculata (ZF) cells containing lipids and smaller cells with the acidophilic cytoplasm with few lipids similar to the zona reticularis (ZR) cells.

The identification of PAs may pose a challenge, as only recently clear criteria for defining the cells that produce aldosterone is found in literature [33]. PAs have varying proportions of four different types of cells. The first consists of clear cells with vacuolated cytoplasm mainly consisting of lipids, having round nuclei that are centrally situated. This aspect resembles that of cells from the ZF. The second type is zona glomerulosa (ZG)-like cells that have lower lipid content. Third type consists of cells that resemble those of the ZR, being eosinophilic and mainly consisting of lipids, having round nuclei that are centrally situated. This aspect resembles that of cells from the ZF. The second type is zona glomerulosa (ZG)-like cells that have lower lipid content. Third type consists of cells that resemble those of the ZR, being eosinophilic and smaller in dimension. Finally, “hybrid” or “intermediate” cells resemble both ZF and ZG components. They have clear microvacuoles with lipid content, as well as eosinophilic cytoplasm that is mainly granular [34, 35]. Literature only cites a small number of adenomas displaying only one cellular type.

Multiple nodules of various sizes can be found both in the affected and in the contralateral adrenal gland, whereas only the gland with the APA often displays hyperplasia of the ZG [33]. Microscopic changes in the structure of the surrounding tissue can be found in patients with APA, either denouncing nodular hyperplasia of the unaffected gland. In some cases, similar changes could also be found in the contralateral glands. These nodules, those are present in the adrenal cortex, of which one can evolve into an APA, have multiple underlying stimuli [20, 36]. A possible explanation for the development of double adenomas would be the sensitization of more than one nodule. Probably, this could be the reason for the identical histopathology of the lesions reported in this paper.

Although HE staining can discriminate between ZG- and ZF-like cells, we are forced to use different specific antibodies to detect enzymes that may influence the formation of aldosterone. This can lead to precise localization of enzymes within pathological adrenals, which could markedly enhance the accuracy of the diagnosis [37]. Moreover, somatic mutations of the potassium voltage-gated channel subfamily J member 5 (KCNJ5) gene show that different mechanisms that take place at a molecular level can regulate the synthesis of aldosterone in APAs [19, 38–40]. However, it seems that more research is needed to reach a conclusion.

Conclusions

Double functioning adrenocortical adenomas in the same gland are very rare. The present paper describes two cases of functioning adrenocortical adenomas causing arterial hypertension. Preoperative diagnosis was difficult in both cases, but corroboration of clinical, biological and CT data allowed for a correct diagnosis. However, histopathology reports achieved to set the final diagnosis of double PAs.

Conflict of interests

The authors declare that they have no conflict of interests.

References


