ISSN 2689-8268 | Volume 5

American Journal of Surgery and Clinical Case Reports

Case Report Open Access

Metachronous Primary Bilateral Macronodular Adrenal Hyperplasia: A Case Report and Review of Literature

Yang LL, Feng Y, Tang JH and Li FP*

Department of Endocrinology, the Seventh Affiliated Hospital of Sun Yat-sen University, China

***Corresponding author:**

Fang P Li, MD, PhD, Professor,
Department of Endocrinology, the Seventh Affiliated Hospital of Sun Yat-sen University, Shen Zhen,518000, China,
E-mail: zsqynfmk2018@126.com

Received: 08 Oct 2022
Accepted: 17 Oct 2022
Published: 21 Oct 2022
J Short Name: AJSCCR

Keywords:

Cushing's syndrome; Primary bilateral macronodular adrenal hyperplasia; metachronous; Treatment; Follow-up; Case report

Citation:

Li FP. Metachronous Primary Bilateral Macronodular Adrenal Hyperplasia: A Case Report and Review of Literature. Ame J Surg Clin Case Rep. 2022; 5(12): 1-5

1. Abstract

1.1. Background: The incidence of endogenous Cushing's syndrome (CS) has been estimated to be approximately 2.5% per million per year in the general population. Primary bilateral macronodular adrenal hyperplasia (PBMAH) is considered a rare cause of CS (<1%). We describe the diagnosis and management of this condition with reference to a clinical case.

1.2. Case Report: A 18-year-old woman with unexplained progressive weight gain was diagnosed with CS in 2002, with an enhanced magnetic resonance imaging scan showing 1.5 × 1.8 cm adrenal nodules on the left. A left adrenalectomy was performed, and the postoperative pathological diagnosis was in line with adrenal cortical nodule adenomatous hyperplasia. About 20 years later, with rounded and reddened face, unexplained progressive weight gain, along with body shape changes and back pain, the woman was diagnosed with CS again. Computed topography scans revealed a nodular thickening of approximately 2.0 × 1.6 cm in the right adrenal gland. After a multidisciplinary discussion, a laparoscopic right partial adrenalectomy was performed successively.

1.3. Conclusion: PBMAH is extremely rare, let alone metachronous hyperplasia. Treatment should be carried out in conjunction with multidisciplinary consultations, and affected patients should be followed up on a life-long basis.

2. Introduction

Cushing's syndrome (CS) is a multisystem disorder that results from inappropriate and excessive glucocorticoid secretion and loss of normal feedback mechanisms in the hypothalamic-pituitary axis [1,2]. The incidence of endogenous CS has been estimated to be approximately 2.5per million per year in the general population, while primary bilateral macronodular adrenal hyperplasia (PBMAH) is considered a rare cause (<1%) of CS and is generally due to bilateral adrenal nodules [3,4].

PBMAH is usually diagnosed according to the clinical symptoms of CS, which are as follows: demonstration of adrenocorticotropic hormone (ACTH)-independent hypercortisolism and bilateral adrenal nodular enlargement on computed tomography (CT) images. Diagnosis of PBMAH may be difficult because hypercortisolism tends to develop slowly, and CS symptoms may take several years to fully unfold. It has been reported that the average length of diagnosis of PBMAH is 7.8 years. PBMAH patients usually present symptoms at 50 to 60 years of age and are often older than those with primary pigmented nodular adrenocortical disease (PPNAD) or Cushing's disease [5]. PBMAH is characterized macroscopically by the presence of macronodules, that is, nodules larger than 1 cm. [6] Herein, we describe the diagnosis and management of a rare clinical case of CS.

3. Case Presentation

A 18-year-old womane reported a weight gain of 8 kg, hypertension, insomnia, weakness, and easy bruising 20 years ago. On examination, she had a blood pressure of 160/100 mmHg and body mass index of 28 kg/m2. A laboratory examination (Table 1) revealed that her urinary free cortisol (UFC) was 101.4 ug/24h (28.5–213.7), and her cortisol was 10.33 ug/dL at 8 am, 10.7 ug/dl at 4 pm, and 11.99 ug/dl at 0 am. Her ACTH level was <6 pg/mL (reference value: 12–78 pg/mL), indicating that her cortisol levels had increased significantly, while her ACTH level had decreased. As the cortisol secretion had increased, she had lost her circadian rhythm. Low-dose dexamethasone suppression test (oral

dexamethasone [0.5 mg] every 6 hours for 2 days) showed that her cortisol suppression was < 50%. The high-dose dexamethasone suppression test (oral dexamethasone [2 mg] every 6 hours for 2 days) showed similar results. Considering ACTH-independent CS, a comprehensive evaluation suggested that the adrenal gland was causing CS. Enhanced Magnetic Resonance Imaging (MRI) was performed to evaluate the adrenal gland, which showed 1.5 × 1.8 cm adrenal nodules on the left. A left adrenalectomy was performed, and postoperative pathological diagnosis was consistent with adrenal cortical nodule adenomatous hyperplasia. The patient experienced transient corticotropic insufficiency immediately after surgery and received temporary hydrocortisone replacement therapy. Her appearance, blood pressure, and weight returned to normal with no further follow-up requirement.

However, she presented to the hospital in 2021 as she presented with a typical cushingoid appearance again, including a moon face with supraclavicular and dorsal fat pads, as well as central obesity and abdominal purplish striae. Her laboratory workup (Table 1) revealed hypercortisolism. Based on the high suspicion of CS, 24-h urine samples for urinary free cortisol (UFC) were collected. Laboratory data revealed UFC 95.43 ug/24 h (reference value: 5.84–40.29 ug/24 h), serum ACTH <1 pg/mL at 8 am (reference value: 9–46 pg/mL), and serum cortisol 21.26 μg/dL at 8 am, 19.48 at 4 pm, 19.44 at 0 am (reference value: <1.8 μg/dL) (Table 1). Following low-dose (0.5 mg every 6 h for 48 h) and high-dose (2 mg every 6 h for 48 h) dexamethasone inhibition tests, no suppression was found on the morning serum cortisol level. Therefore, ACTH-independent CS was considered. CT showed nodular thickening of approximately 2.0 × 1.6 cm in the right adrenal gland (Figure 1), and the left adrenal glands were absent, showing postoperative changes (Figure 2). Considering the differentiation of adrenal adenoma and hyperplasia, an MRI was recommended, and dynamic pituitary MRI was performed. This showed left adrenal gland changes after surgery, thickening of the nodules of the right adrenal gland (1.9 × 1.5 cm), and hyperplasia. One internal limb nodule showed reduced enhancement on the delayed scan, and the adenoma was waiting to be discharged.

Her final diagnosis was Metachronous primary bilateral macronodular adrenal hyperplasia.

After a multidisciplinary discussion, laparoscopic right adrenal tumor resection was performed. The operation was successful and the level of cortisol at 8 am had reduced to 5.43 ug/dl at 1 week after the operation. The pathological diagnosis was nodular hyperplasia of cortical cells that could be perceived locally in the adrenal tissue, with no clear capsule identified around the nodule, consistent with nodular hyperplasia of the adrenal cortex. DNA extracted from blood leukocytes and adrenal nodules was sequenced for the whole genome, but no related genes were found.

After the operation, glucocorticoid replacement therapy was uneventfully reduced to hydrocortisone 40 mg/day and tapered; the patient was hospitalized for 1.5 months after the operation; her moon face appearance had been cured, her back pain healed, and she presented as euthymic. Considering ACTH-independent CS, her blood pressure was 127/93 mmHg (without antihypertensive drugs); her cortisol serum level was 4.52 μg/dL, and she was, thereafter, independent of steroid medication. Three months later, her hydrocortisone dose was reduced to 20 mg/day, with a blood pressure of 120/80 mmHg.

Table 1: Laboratory data of the present patient

Variable, unit	Value	Reference range
in 2002		
<Blood examination>		
Fasting plasma glucose, mmol/l	5.3	2.9-6.1
Hemoglobin A 1 c, %	5	4.9–6.0
ACTH (08am), pg/mL	<6	Dec-78
Cortisol (08am), μg/dL	10.33	
Cortisol (4pm), μg/dL	10.7	
Cortisol (0am), μg/dL	11.99	
Aldosterone,pg/ml	54.09	
Renin activity	1.41	
<Urine analysis>		
free cortisol, ug/24h	70.95	28.5-213.7
Dexamethasone suppression tests		
Dexamethasone	low-dose	high-dose
Cortisol (ug/dL)	10.05	11.02
in 2021		
<Blood examination>		

Fasting plasma glucose, mmol/l	4.9	2.9-6.1
Hemoglobin A 1 c, %	6.1	4.9–6.0
3-Methoxytyramine(nmol/l)	<0.08	<0.18
Methadrenaline(nmol/l)	<0.08	<0.5
Methoxy norepinephrine(nmol/l)	0.28	<0.9
Parathyroid hormone(pg/ml)	57.83	15-65
Testosterone(ng/dl)	31.02	Oct-75
Aldosterone(pg/ml)	2.15	0-35.3
Direct renin concentration(mU/L)	2.313	4.4-46.1
ACTH (08am), pg/mL	<1	7.2-63.3
Cortisol (08am), µg/dL	21.26	
Cortisol (4pm), µg/dL	19.48	
Cortisol (0am), µg/dL	19.44	
Aldosterone,pg/ml	54.09	
Renin activity	1.41	
<Urine analysis>		
free cortisol, ug/24h	640.44	4.3-176
<Dexamethasone suppression test, Liddle's method>		
No DEX Urinary- free cortisol, ug/24h	1345	
2mg/day of DEX, the second day Urinary- free cortisol, nmol/day	1081	
8mg/day of DEX, the second day Urinary- free cortisol,nmol/day	1634	
No DEX 8am Serum cortisol, ug/dl	20.57	
2mg/day of DEX, the first day Serum cortisol, ug/dl	19.33	
2mg/day of DEX, the second day Serum cortisol, ug/dl	22.27	
8mg/day of DEX, the first day 8am Serum cortisol,ug/dl	19.67	
8mg/day of DEX, the second day 8am Serum cortisol,ug/dl	22.07	
<after operation >		
Serum Cortisol (08am), µg/dL	5.43	

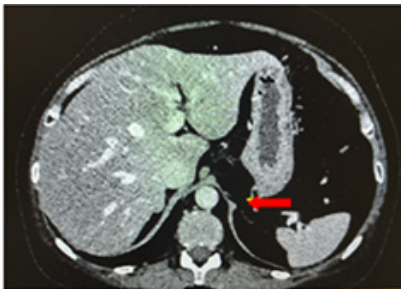

Figure 1: Computed tomography of the abdomen and pelvis showing absence of left adrenal gland

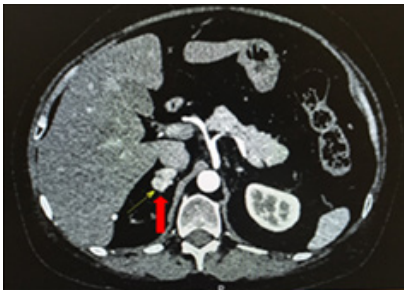

Figure 2: Computed tomography of the abdomen and pelvis showing right adrenal nodules

4. Discussion

Clinically, CS of the PBMAH type is characterized by marked bilateral enlargement of the adrenal glands and aberrant cortisol secretion responses upon challenge with exogenous stimuli [7]. It may present with simultaneous or metachronous hyperplasia of both adrenal glands [8]. More rarely, PBMAH may also be asymmetric and, in some cases, unilateral [9]. This patient initially presented with asynchronous nodular hyperplasia in one gland and 20 years later in the contralateral gland. PBMAH predominantly affects women, but the sex ratio is balanced in patients with identified genetic causes, and the median age at diagnosis in sporadic cases is approximately 55 [10,11]. The patient was diagnosed with PBMAH at 18 years of age. An important differential diagnosis is PPNAD, in which the age of onset is earlier, with an average age of onset at 18 years. It presents with multiple nodules in the lateral adrenal glands, generally <3 mm in diameter, forming "beads-like" structures in radiological images [12]. The pathological features are multiple pigmented cortical nodules and internodal cortical atrophy, with no envelope around the nodules, and fat brown pigmentation in the cytoplasm [13]. These features help distinguish it from PBMAH.

PBMAH has long been referred to as 'ACTH-independent macronodular adrenal hyperplasia', but the recent discovery of an intra-adrenal ACTH synthesis responsible for local stimulation of cortisol production made the former appellation obsolete [9]. Studies have shown that the secretion of cortisol is regulated by ACTH produced by adrenal cortex tissue. The expression of ACTH in hyperplastic adrenal tissue is not caused by the differentiation of adrenal chromaffin-like, lymphocyte-like, or pituitary ACTH-like cells. However, it exhibits steroid production. The morphological characteristics of the cells are always labeled with a steroid-producing factor 1 antibody [14].

Few rare cases of PBMAH are part of other genetic tumor predisposition syndromes, including multiple endocrine neoplasia type 1, familial adenomatous polyposis, and hereditary leiomyomatosis (fumarate hydrogenase). However, these alterations only explain a very small proportion of PBMAH cases and are naturally associated with other tumors [15]. It is suspected that cAMP/PKA pathway overactivity is involved in many cases of adrenal tumors, including PBMAH, in which germline variants of PDE11A have been observed more frequently than in the general population [16]. PBMAH is frequently a genetic disorder, most often caused by inactivating mutations of ARMC5, a putative tumor suppressor gene [17], involved in the regulation of steroidogenic enzymes, including glucocorticoid synthesis [18].Germline and somatic mutations have also been reported to be involved in the mechanism of PBMAH. Genes associated with PBMAH include armadillo repeat containing 5 (ARMC5), phosphodiesterase 11A (PDE11A), adenomatous polyposis coli (APC), and fumarate hydratase (FH) [19]. It has been reported that the pathogenic germline mutations of ARMC5 account for 55% of PBMAH patients [20], and patients with ARMC5 germline mutations exhibit more severe disease, including cortisol excess, increased adrenal size and number of adrenal nodules, and frequency of the metabolic complications of CS [21]. However, we did not find any related gene mutations. When PBMAH is treated, the standard treatment is bilateral adrenalectomy, but the risk is very high and prone to adrenal crisis [22]. Therefore, some surgeons believe that unilateral total adrenalectomy and possibly adrenal-sparing surgery are good and safe surgical methods [23,24]. It is also possible to perform total adrenal resections and subtotal resections of the contralateral adrenal gland [25]. In the present case, we performed a left adrenalectomy 18 years ago, a laparoscopic right partial adrenalectomy was conducted at recurrence, the patient's symptoms resolved, and the hydrocortisone dose was tapered.

5. Conclusion

PBMAH is a rare and special type of CS, let alone metachronous hyperplasia. We need to identify such types early and arrange short-interval follow-ups after treatment. Multidisciplinary discussion is necessary before treatment. Unilateral total adrenalectomy and possibly adrenal-sparing surgery are safe and helpful procedures for treating PBMAH.

References

1. Newell-Price J, Bertagna X, Grossman AB, et al. Cushing's syndrome. Lancet. 2006; 367(9522): 1605-17
2. Pluta RM, Burke AE, Golub RM. JAMA patient page.Cushing syndrome and Cushing disease. JAMA. 2011; 306(24): 2742.
3. Antonini SR, Fragoso MC, Lacroix A. Clinical and molecular aspects of the ACTH-independent bilateral macronodular adrenal hyperplasia. Arq Bras Endocrinol Metabol. 2004; 48(5): 620-636.
4. Venanzi AD, Alencar GA, Bourdeau I, et al. Primary bilateral macronodular adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes. 2014; 21(3):177-184.
5. Lin W, Huang HB, Wen JP, et al. Approach to Cushing's syndrome in pregnancy: two cases of Cushing's syndrome in pregnancy and a review of the literature. Ann Transl Med. 2019;7(18):490.
6. Stratakis CA. Cushing syndrome caused by adrenocortical tumors and hyperplasias (corticotropin-independent Cushing syndrome). Endocr Dev. 2018; 13: 117-32.
7. Tanaka S, Fujishiro M, Nakamura Y, et al. Retention of aberrant cortisol secretion in a patient with bilateral macronodular adrenal hyperplasia after unilateral adrenalectomy. Ther Clin Risk Manag. 2019; 15: 337-42.
8. Venanzi AD, Alencar GA, Bourdeau I, et al. Primary bilateral macronodular adrenal hyperplasia. Current Opinion in Endocrinology & Diabetes and Obesity. 2014; 21(3): 177-84.
9. Bonnet-Serrano F, Bertherat J. Genetics of tumors of the adrenal cortex. Endocr Relat Cancer. 2018; 25(3): 131-52.
10. Espiard S, Drougat L, Libé R, et al. ARMC5 mutations in a large

cohort of primary macronodular adrenal hyperplasia: clinical and functional consequences. J. Clin. Endocrinol. Metab. 2015; 100(6): E926–E935.

11. Albiger NM, Regazzo D, Rubin B, et al. A multicenter experience on the prevalence of ARMC5 mutations in patients with primary bilateral macronodular adrenal hyperplasia: from genetic characterization to clinical phenotype. Endocrine. 2017; 55(3): 959-68.
12. Shi Chen, Ran Li, Lin Lu, et al. Efficacy of dexamethasone suppression test during the diagnosis of primary pigmented nodular adrenocortical disease in Chinese adrenocorticotropic hormone-independent Cushing syndrome. Endocrine. 2018; 59(1): 183-90.
13. Manipadam MT, Abraham R, Sen S, et al. Primary pigmented nodular adrenocortical disease.J Indian As soc Pediatr Surg. 2011; 16(4):160-2.
14. Louiset E, Lefebvre H. Intraadrenal corticotropin in bilateral macronodular adrenal hyperplasia. N Engl J Med. 2014; 370(11): 1071-2.
15. Ohashi A, Yamada Y, Sakaguchi K, et al. A natural history of adrenocorticotrophin-independent bilateral adrenal macronodular hyperplasia (AIMAH) from preclinical to clinically overt Cushing, s syndrome. Endocr J. 2001; 48(6): 677-83.
16. Bouys L, Chiodini I, Arlt W, et al. Update on primary bilateral macronodular adrenal hyperplasia (PBMAH). Endocrine. 2021; 71(3): 595-603.
17. Lodish M, Constantine A. Stratakis. A genetic and molecular update on adrenocortical causes of Cushing syndrome. Nature Reviews Endocrinology. 2016; 12(5): 255-62.
18. Conceição BBD, Cavalcante IP, Kremer JL, et al. ARMC5 mutations are associated with high levels of proliferating cell nuclear antigen and the presence of the serotonin receptor 5HT4R in PMAH nodules.Arch Endocrinol Metab. 2020; 64(4): 390-401.
19. Yu L, Zhang J, Guo X, et al. ARMC5 mutations in familial and sporadic primary bilateral macronodular adrenal hyperplasia. PLoS One. 2018; 13(1): e0191602.
20. Assie G, Libe R, Espiard S, et al. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing, syndrome. NEngl J Med. 2013; 369(22): 2105-14.
21. Lucas B, Iacopo C, Wiebke A, et al. Update on primary bilateral macronodular adrenal hyperplasia (PBMAH). Endocrine. 2021; 71(3): 595-603.
22. Corcuff JB, Young J, Masquefa-Giraud P, et al. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. Eur J Endocrinol. 2015; 172(4): 473-81.
23. Li J, Yang CH. Diagnosis and treatment of adrenocorticotrophic hormone-indepent macronodular adrenocortical hyperplasia: A report of 23 cases in a single center. Exp Ther Med. 2014; 9(2): 507-12.
24. Meloche-Dumas L, Mercier F, Lacroix A. Role of unilateral adrenalectomy in bilateral adrenal hyperplasias with Cushing's syndrome. Best Practice & Research Clinical Endocrinology & Metabolism. 2021; 35(2): 101486.
25. Albiger NM, Ceccato F, Zilio M, et al. Ananalysis of different therapeutic options in patients with Cushing's syndrome due to bilateral macronodular adrenal hyperplasia: a single-centre experience. Clin Endocrinol(Oxf). 2015; 82(6): 808-15.