An Overview of the Heterogeneous Causes of Cushing Syndrome Resulting From Primary Macronodular Adrenal Hyperplasia (PMAH)

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Abstract

Primary macronodular adrenal hyperplasia (PMAH) is considered a rare cause of adrenal Cushing syndrome, its pituitary ACTH-independent, generally results from bilateral adrenal macronodules (>1 cm), and is often associated with variable cortisol secretion, resulting in a heterogeneous and complex adrenal disease. Different molecular mechanisms involving the actors of the cAMP/protein kinase A pathway have been implicated in the development of PMAH, including germline and/or somatic molecular defects such as hyperexpression of the G-protein receptor genes and variants of MC2R, GNAS, PRKAR1A, and PDE11A. Nevertheless, since 2013, the ARMC5 gene is believed to be a major genetic cause of PMAH, accounting for more than 80% of the familial forms of PMAH and 30% of apparently sporadic cases, also in food-dependent Cushing syndrome in which ARMC5 is not involved. Recently, 2 independent groups have identified that the tumor suppressor gene KDM1A is responsible for PMAH associated specifically with food-dependent Cushing syndrome. Consequently, PMAH has been more frequently genetically associated than previously assumed. This review summarizes the most important aspects, including hormone secretion, clinical presentation, radiological imaging, and molecular mechanisms, involved in familial Cushing syndrome associated with PMAH.

Key Words: ARMC5, KDM1A, macronodular adrenal hyperplasia, PMAH

Abbreviations: 18F-FDG, 18F-fluorodeoxyglucose; CS, Cushing syndrome; CT, computed tomography; FAP, familial adenomatous polyposis; Gs-protein, stimulatory G-protein; MRI, magnetic resonance imaging; PET, positron emission tomography; PKA, protein kinase A; PMAH, primary macronodular adrenal hyperplasia

As first described by Kirschner et al [1] in 1964, primary macronodular adrenal hyperplasia (PMAH) is characterized by the presence of functional adrenal macronodules with variable cortisol secretion, independent of the pituitary ACTH stimulation. The clinical presentation ranges from a metabolic syndrome to classical Cushing syndrome (CS), depending on long-term cortisol hypersecretion and the hormone level concentration. Since its first description, PMAH has received different names, such as nodular hyperplasia of the adrenal gland [2], ACTH-independent massive bilateral adrenal disease [3], massive macronodular hyperplasia [4], giant macronodular adrenal hyperplasia [5], huge bilateral adrenocortical multinodular hyperplasia [6], macronodular adrenal hyperplasia [7], ACTH-independent macronodular adrenal hyperplasia [8], and bilateral primary macronodular adrenal hyperplasia [9]. The bilateral nature of adrenal macronodules in PMAH is considered one of its most common features; therefore, the asymmetric and asynchronous development of adrenal nodules can also occur [10]. In 2013, Louiset et al demonstrated ectopic ACTH in clusters of adrenal nodules with autocrine and paracrine actions involving cortisol secretion [11]. Thus, PMAH appears to be a more appropriate term to comprehensively designate this heterogeneous adrenal disease [10].

Epidemiology

PMAH is a rare cause of adrenal CS, accounting for fewer than 2% of all endogenous etiologies of CS [2]. PMAH is currently believed to be underdiagnosed, with a higher frequency than previously thought. This hypothesis is supported by the increasing diagnosis of PMAH in asymptomatic patients or in those with mild hypercortisolism associated with adrenal incidentaloma or in investigation of relatives of index cases [12].

To date, 45 families (170 individuals) with a female:male ratio of 1.24 have been described between 1993 and 2020. The median age at diagnosis of index cases (for females and males) is approximately 55 years, with CS accounting for 73% of clinical presentation (Supplemental Table S1) [13].

Pathophysiology

PMAH can be associated with genetic syndromes or present in isolated forms, such as familial cases or apparently sporadic cases.

The pathophysiological process that culminates in PMAH has not been fully elucidated. It is a heterogeneous disease
associated with different germline and/or somatic genetic alterations, involving different actors of molecular signaling of the cAMP/protein kinase A (PKA) pathway and others tumor suppressor genes. However, these events occur only in a few cases. The main genes involved in the etiology of PMAH as well as potentially molecular signaling pathways are listed in Table 1 [8, 10, 14-28].

Abnormal Regulation of the Adrenal Cortex by Aberrant Hormone Receptors

Under physiological conditions, pituitary ACTH is the main regulator of cortisol and androgen synthesis by the adrenal cortex. The ACTH molecule binds to MC2R in the adrenal cortex. MC2R is mediated by stimulatory G-protein (Gs-protein) that activates the cAMP/PKA signaling pathway, culminating in adrenal steroidogenesis. In PMAH, cortisol synthesis occurs independent of pituitary ACTH stimulation or MC2R. The production of cortisol would be regulated by aberrant (or illicit) hormonal receptors located within the adrenal cortex and coupled to the G-protein (Gs and Gq/i). The stimulation of these receptors by their respective ligands would trigger the activation of the cAMP/PKA signaling pathway, with consequent stimulus to steroidogenesis and adrenal gland hyperplasia. Different aberrant hormone receptors (Table 2) have been documented in PMAH [29, 30].

However, it is still unclear whether the overexpression of these aberrant hormone receptors in the adrenal cortex is an initial and essential event in the pathogenesis of PMAH or a secondary event resulting from cell proliferation and dedifferentiation [10, 31] (Fig. 1).

Ectopic production of ACTH in Adrenal Macronodules

In 2013, Louiset et al demonstrated that cortisol secretion by adrenal macronodules in PMAH is regulated by ACTH produced by clusters of hyperplastic steroidogenic cells present in adrenal macronodules [11]. This ectopically produced ACTH acts in an autocrine and paracrine manner, activating MC2R receptors on steroidogenic cells and culminating in cortisol production. It was also demonstrated that in patients with aberrant hormone receptors, activation of these receptors by their respective ligands induces ACTH secretion by hyperplastic steroidogenic cells, in addition to stimulating direct cortisol production. This suggests an indirect mechanism of amplification of the stimulation to cortisol hormone secretion [11]. It is also speculated that ectopic ACTH secretion plays an antiapoptotic role; therefore, it induces adrenal gland hyperplasia [32].

Activating Germline Mutation of the MC2R Gene (Melanocortin 2 Receptor)

The germline activating mutation of the MC2R gene is an extremely rare cause of PMAH, with only 1 patient being diagnosed with it. This mutation determines the constitutive activation of the adenylate cyclase/cAMP/PKA signaling pathway, leading to hyperplasia and autonomous cortisol secretion by the adrenal gland [15].

Amplification of PRKACA

PRKACA encodes the α catalytic subunit of PKA. In 2 patients with PMAH (mother and child), germination duplication of the p13.2-p13.12 genomic region of chromosome 19 was demonstrated, with consequent amplification of PRKACA located in this region [16]. The duplication of PRKACA leads to increased expression of its protein, resulting in an increase in the PKA activity and its subsequent signaling pathway [17].

Allelic Variants of the PDE11A gene

Germline inactivating missense variants in PDE11A increase intracellular cAMP, activating the cAMP/PKA signaling pathway. These variants are implicated in the genetic etiology of isolated micronodular adrenal hyperplasia. Some allelic variants of the PDE11A were found in patients with PMAH at a higher frequency than in the control population, leading to the hypothesis of the association of these allelic variants with the etiology of PMAH [18]. However, they are classified as polymorphic variants; therefore, they are also found in the general population. It is unlikely that these allelic variants are directly involved in the etiology or genetics of PMAH. However, it is impossible to rule out that these polymorphisms can modulate the phenotype of patients with PMAH.

PMAH in the Context of Genetic Syndromes

PMAH has also been observed to be associated with genetic syndromes like multiple endocrine neoplasia type 1, familial adenomatous polyposis, hereditary leiomyomatosis, renal cell carcinoma, and McCune–Albright syndrome (Table 2). Nevertheless, no mutations in related genes, such as MEN1, APC, and FH, are found when PMAH occurs outside the context of these genetic syndromes [31, 32].

Multiple Endocrine Neoplasia Type 1

MEN1 is caused by the tumor suppressor gene MEN1 (chromosome 11q13.1), which is involved in the control of the cell cycle and proliferation. Adrenocortical bilateral lesions are frequent among patients with MEN1 or with sporadic neuroendocrine tumors documented in approximately 20% of patients [20].

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease related to the tumor suppressor gene APC (chromosome 5q22.2). It acts as an antagonist of the Wnt signaling pathway, which is also involved in the control of cell proliferation and differentiation, regulation of cell adhesion and migration, and stabilization of chromosomal segregation. Adrenocortical lesions (adenomas, carcinomas, and PMAH) occur 2 to 4 times more frequently in patients with FAP compared with the general population [33]. Few studies have revealed the loss of heterozygosity of APC in adrenal hyperplasia [34]. The signaling pathway might be a factor in the pathophysiology of PMAH; however, germline and somatic pathogenic variants of the APC have been described only in the context of PMAH associated with FAP [23].

Hereditary Leiomyomatosis and Renal Cell Carcinoma

Hereditary leiomyomatosis and renal cell carcinoma are caused by inactivating mutations of the tumor suppressor gene FH (OMIM 136850, 1q43) [35]. Inactivation of FH determines the activation of hypoxia-induced factor 1, which favors increased glycolytic activity, neovascularization, and downregulation of cellular apoptosis, as well as all significant features of tumorigenesis [36]. To date, there are few reports of genetic variations in the FH; however, it could be a candidate gene involved in PMAH [37].
# Table 1. Main genes involved in syndromic and nonsyndromic PMAH

| Genes | Name/OMIM* | Genetic syndrome | Pathogenic variants | Probable mechanism |
|-------|------------|------------------|--------------------|-------------------|
| MC2R (1,2) | Melanocortin-2 receptor (OMIM 607397) | PMAH | Germline activation | Constitutive activation of the ACTH receptor and consequent activation of the adenylate cyclase/cAMP/protein kinase A signaling pathway. |
| PRKACA (3,4) | Protein kinase, cAMP-dependent, catalytic, alpha (OMIM 601639) | Adrenal tumors—PMAH | Genomic duplications | Increased expression of the α catalytic subunit of protein kinase A and consequent activation of its signaling pathway. |
| PDE11A (5,6) | Phosphodiesterase 11A (OMIM604961) | Adrenal tumors—PMAH | Germline inactivation | Altering cAMP degradation (catalyzes the hydrolysis of cAMP and cGMP). |
| MEN1 (7) | Multiple endocrine neoplasia 1 (OMIM 613733) | Multiple endocrine neoplasia 1 | Germline inactivation | Inactivation of tumor suppressor gene, inducing cell proliferation mediated by different molecular mechanisms. |
| APC (8) | Adenomatous polyposis coli (OMIM 611731) | Familial adenomatous polyposis | Germline and somatic inactivation | Inactivation of tumor suppressor gene, with consequent activation of the WNT/β-catenin signaling pathway, inducing cell proliferation. |
| FH (9) | Fumarate hydratase (OMIM 136850) | Hereditary leiomyomatosis and renal cell cancer | Germline and somatic inactivation | Inactivation of tumor suppressor gene, leading to activation of the hypoxia-induced transcription factor signaling pathway, stimulating cell proliferation. |
| GNAS (10-12) | GNAS complex locus (OMIM 139320) | McCune-Albright syndrome: isolated PMAH | Somatic activation (post-zygotic) | Loss of intrinsic GTPase activity of the α-subunit of the stimulatory G-protein and consequent activation of the adenylate cyclase/cAMP-protein kinase A pathway. |
| ARMC5 (13-15) | Armadillo repeat-containing protein 5 | PMAH: familial and apparently sporadic cases (OMIM 615549) | Germline and somatic inactivation | Inactivation of tumor suppressor gene, inducing cell proliferation and possible activation of the WNT/β-catenin signaling pathway. |
| KDM1A/LSD1 (16,17) | Lysine Demethylase 1A; Lysine-specific demethylase 1 (OMIM609132) | GIP-dependent Cushing syndrome; familial and apparently sporadic cases | Germline and somatic inactivation | Demethylating histone H3 on lysine 4 and cause gene repression. Also inhibit the role of p53 in promoting apoptosis. |

Abbreviations: cGMP, cyclic guanosine monophosphate; PMAH, primary macronodular adrenal hyperplasia.

*OMIM (Online Mendelian Inheritance in Man), available in https://omim.org/.
Activating of the GNAS Somatic Mutations

Activating postzygotic somatic mutations in the GNAS gene, which encodes the Gs-protein alpha subunit, determine the constitutive activation of the adenylate cyclase/cAMP/PKA signaling pathway, leading to McCune–Albright syndrome. These mutations, despite being infrequent, have already been described in PMAH in the absence of other typical manifestations of McCune–Albright syndrome manifestations and may represent a variant of this syndrome or even late somatic mutations [8, 23, 38]. CS occurs in approximately 7% of the children with McCune–Albright syndrome, mainly in the first year of life. The most common pathological finding in these children is nodular adrenal hyperplasia [24].

PMAH From ARMC5 Germline Pathogenic Variants

Germline heterozygous mutations in the ARMC5 are present in 10% to 55% of patients with PMAH, thus constituting the main genetic cause of the disease [10, 25, 31]. The
demonstration of a second somatic inactivating mutation in the ARMC5 in hyperplasia adrenal tissue suggests that this gene acts as a tumor suppressor gene [10, 25]. Initial functional studies demonstrated that ARMC5 has a role in the inhibition of cell proliferation and in the regulation of steroidogenesis [25]. Inactivating mutations in ARMC5 appear to reduce the stimulus for adrenal steroidogenesis while compromising its proapoptotic activity. This seemingly contradictory property supports the thesis that hypercortisolism in PMAH is related to adrenocortical cell hyperplasia rather than more efficient steroidogenesis [25, 39]. The ARMC5 protein is formed by an N-terminal domain of armadillo repeats and a C-terminal Brac-a-Brac domain (Tramtrack, Broad-complex). Both domains serve as an anchoring platform for different substrates (proteins). It has been disclosed that mutations in the Brac-a-Brac domain of the ARMC5 protein prevent its ubiquitin-dependent proteasomal degradation mediated by the Cullin3 protein. Moreover, it is theorized that other substrates (eg, oncogenic proteins) anchored to the mutated ARMC5 protein would not be consequently degraded, favoring the cell-cycle advancement. However, mutations in the domain of armadillo repeats or even in other regions of the ARMC5 protein could hinder the anchoring of different substrates (eg, other oncogenic proteins), preventing their degradation by the ubiquitin-proteasome system through the ARMC5 protein. However, this last assumption still needs to be evaluated. Other studies conducted in animal models have delineated that mutations in ARMC5 could be associated with the activation of the WNT/β-catenin signaling pathway [40].

As previously mentioned, abnormal G-protein receptor expression has been associated with PMAH, and loss of ARMC5 function has been associated with abnormal responses to upright posture, vasopressin, and metoclopramide tests, as seen in a large ARMC5 family with aberrant adrenergic and V1-vasopressin receptors, implying a link between germline ARMC5 pathogenic variants and abnormal G-protein receptor expression. These findings support the theory that ARMC5 inactivation is directly responsible for G-protein receptor overexpression [10, 25, 41, 42]. However, no study has demonstrated the exact molecular mechanism involved between the loss of function of ARMC5 and the overexpression of G-protein receptors yet [39, 40, 43].

Germline and somatic mutations have been described throughout ARMC5. However, it remains unclear whether there would be a genotype–phenotype correlation [31]. It was possible to demonstrate that the disease has an autosomal dominant inheritance pattern, with late and incomplete penetrance, from a study of a large Brazilian family with PMAH and associated with ARMC5 mutations (ie, some individuals with ARMC5 mutations may not express the clinical/radiological characteristics of the disease despite being elderly individuals with long-term follow-up [10]). Thus, it is likely that other genetic and molecular alterations modulate the phenotypic expression of PMAH.

Interesting, 1 study reported 16 different ARMC5 germline variants in 68.4% of the patients with MEN1 and spNETs, including 2 predicted as damaging. The status of loss of heterozygosity on chromosome 16p and ARMC5 germline variants were present together in 67.6% tumors and in 30.4% associated with biallelic inactivation of ARMC5. The authors suggested that ARMC5 plays a role in modifying the phenotype of patients with spNETs and MEN1 beyond its known role in PMAH [44]. However, these data need to be validated in other cohorts.

**New Genetic Insights**

Recently, Vaczlavik et al used an integrated genomic approach to demonstrate new etiologies of PMAH using adrenal hyperplasia tissue and studying their clinical and pathological features. The authors identified 3 molecular groups with different clinical features: G1, with ARMC5 inactivating variants; G2, with food-dependent CS characterized by gastric inhibitory polypeptide receptor ectopic expression; and G3, a compound in patients with mild hypercortisolism phenotypes. Interestingly, the germline truncating variants of KDM1A were observed in 5 of 6 patients in G2; they were always associated with a somatic loss of KDM1A as a secondary molecular event, leading to a loss of KDM1A expression at the mRNA and protein levels [27]. Additionally, KDM1A pathogenic variants were identified in 4 additional indexed cases with food-dependent CS.

Chasseloup et al also identified germline inactivating pathogenic variants in KDM1A in 17 PMAH patients diagnosed with food-dependent CS with overexpression of the gastric inhibitory polypeptide receptor through a similar genetic mechanism. Moreover, 3 (18%) patients belonged to 2 unrelated families. No ARMC5 variants were detected in patients with gastric inhibitory polypeptide-dependent PMAH in this study. Thus, genetic alterations in ARMC5 and KDM1A appear to be mutually exclusive molecular events, accounting for the development of adrenal hyperplasia and cortisol secretion in PMAH [28].

Additionally, KDM1A is abnormally overexpressed in acute myeloid leukemia and is involved in families with a history of multiple myeloma and solid tumors, where it promotes proliferation, inhibits differentiation, and enhances cell motility [27, 45]. For carriers of KDM1A pathogenic variants, besides clinical examination and biochemical screening for food-dependent CS, a serum protein electrophoresis is mandatory to detect potential monoclonal gammopathy [28]. Investigation in a large cohort will clarify the frequency of this new gene associated with PMAH and the prevalence of hereditary predisposition to hematopoietic neoplasm [46].

**Pathology**

PMAH is a benign disease and, so far, there have been no reports on the malignant transformation of adrenal lesions [29]. To the best of our knowledge, only 1 case has reported a bilateral adrenal mass with a unilateral high uptake on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) scan. Pathological analysis revealed bilateral adrenal hyperplasia with adrenocortical carcinoma, suggesting a co-occurrence [47], corroborating Cavalcante’s findings [48].

Macroscopically, an increase in the size of the adrenals was observed, with the presence of yellowish macronodules (>1 cm), and in generally the total weight of adrenals is greater than 60 g and each gland may weigh more than 200 g [49] (Fig. 2).

Microscopic examination of adrenal glands in PMAH reveals the presence of multiple homogeneous nodules, predominantly constituted by the following 2 distinct cell groups: 1 formed by cells with clear cytoplasm (rich in lipids),
arranged in cords, and another consisting of cells with compact cytoplasm (poor in lipids), arranged in structures like nests or islands (Fig. 2). Studies using in situ hybridization and immunohistochemistry demonstrated the expression of enzyme 3β-hydroxysteroid dehydrogenase type 2, exclusively in large cells with clear cytoplasm, and of enzyme 17α-hydroxylase/17,20-lyase, expressed mainly in small cells with compact cytoplasm [50]. Additionally, ACTH is ectopically expressed in both cell types: clear cytoplasm (rich in lipids) cells and compact cytoplasm cells (poor in lipids) [11].

PMAH Presentation

PMAH can be sporadic or inherited (autosomal dominant inheritance pattern with incomplete penetrance). The diagnosis of inherited PMAH became more frequent after the discovery of germline pathogenic variants in the ARMC5 gene [10, 25].

Systematic investigation of germline variants in patients demonstrated that many cases of the disease, initially classified as sporadic, were inherited. A careful study of the relatives of index cases permitted the diagnosis of many unsuspected familial cases of the disease, including asymptomatic cases [10]. In addition, the incidental diagnosis of PMAH has also become more frequent because of increasing access to diagnostic imaging technologies [43]. Thus, until recently, overt CS was believed to be the main manifestation of PMAH [51]. Nevertheless, current evidence suggests that subclinical hypercortisolism is the most frequent presentation of the disease [10, 43].

In most studies, PMAH is described with equal prevalence in both sexes with a slight female predominance, especially among sporadic cases [10, 43]. The clinical evolution of PMAH is usually slow over many years and is related to the insidious progression of hypercortisolism. Generally, the disease clinically manifests around the fifth to sixth decades of life [52]. It is still unclear whether the evolutionary behavior and expressiveness of the disease would be different in the sporadic and inherited forms of PMAH. However, patients with ARMC5 pathogenic variants present a more aggressive hypercortisolism status [53].

Laboratory Diagnosis

The main laboratory investigations for suspected patients are as follows: serum cortisol after 1 mg overnight dexamethasone suppression test (sensitivity and specificity of 90% and 87.3%, respectively) [41], midnight salivary cortisol, 24-hour free urinary cortisol (sensitivity of 26.7% and 14.3%, respectively), and plasma ACTH.

Figure 2. Primary macronodular adrenal hyperplasia. Macroscopically (A), adrenal enlargement and the presence of yellowish nodules protruding from the glandular contours were observed. Under microscopy, it is possible to observe 60% of compact cells (B) and 30% of clear cells (C). Source: Primary macronodular adrenal hyperplasia patient archive at the HCFMUSP Suprarenal Unit.
long-term control of hypercortisolism or even the reversal of the gland hyperplasia in most cases [41].

In some isolated cases of PMAH, in addition to cortisol synthesis, there is a concomitant secretion of aldosterone by the hyperplasia. The actual prevalence of this association is still unknown, but it must be considered during patient assessment [55]. The concomitant secretion of androgens or estrone in PMAH is very rare [29].

Meningioma Associated With PMAH

ARMC5 presents a wide expression in various tissues, suggesting that ARMC5 plays a role in the pathogenesis of diseases involving other tissues beyond the adrenal gland [36].

In 2005, Lee et al incidentally found and described 2 sisters with PMAH and abnormal G-protein receptors with meningiomas [57], after which we proved that the patients with PMAH and ARMC5 variants had a higher risk of developing intracranial meningiomas [10]. These tumors were present in 33% (5/15) of PMAH patients undergoing magnetic resonance imaging (MRI) [18, 41]. Another study found a second-hit variation of ARMC5 in meningioma tissue from a patient with PMAH, further supporting the suspicion that ARMC5 is associated with the occurrence of these tumors [58]. Nowadays, for the early diagnosis of these intracranial tumors, MRI scanning of the central nervous system is suggested to investigate the presence of meningiomas in patients with PMAH [18, 41]. However, the frequency of the radiological workup needs to be established.

Radiological Diagnosis

CT and MRI usually reveal enlargement of the adrenal glands in PMAH associated with the presence of bilateral nodules of approximately 1 to 5 cm in diameter [29]. Additionally, diffuse adrenal gland enlargements without a clear distinction between the nodules and the presence of asymmetry between the 2 glands have been described. In the early stages of the disease, approximately one-third of patients have radiological changes in just a single adrenal gland [10].

On the CT (precontrast phase) examination of PMAH, adrenal nodules can often have a greater density than is usually demonstrated by adrenocortical adenomas. One study indicated that approximately 61% of the adrenal macronodules manifested a density over 10 HU and 30% manifested a density beyond 20 HU [41]. Hyperplastic adrenals were hypointense in relation to the liver and isointense in relation to the muscle on T1-weighted MRI sequences. Moreover, on T2-weighted sequences, adrenals in PMAH are usually hypointense in relation to the liver. Images obtained in an out-of-phase sequence (chemical-shift technique) are commonly used to depict signal loss, which is consistent with a higher intracellular lipid content [59, 60].

Despite being a benign disease, PMAH frequently demonstrates an increase in 18F-FDG-PET/CT uptake. This uptake attains levels similar to those frequently observed in malignant and metastatic lesions (maximum standardized uptake value > 3.1), reflecting the high glycolytic activity of nodular lesions [61] (Fig. 3).

Surgical Treatment

The main treatment recommended for PMAH associated with overt CS is bilateral adrenalectomy, followed by therapeutic replacement of glucocorticoids and mineralocorticoids throughout life [29, 43].

Unilateral adrenalectomy of the most hyperplastic gland has been proposed as a safe and alternative treatment, especially in the following situations [62]:

- Mild hypercortisolism (autonomous cortisol secretion) associated with comorbidities potentially related to excessive hormonal secretion and worsening of metabolic syndrome.
- Patients who are more likely to become non-compliant to glucocorticoid replacement (eg, patients with psychiatric disorders, cognitive deficits, impairing social issues).

However, the possibility of mild persistent hypercortisolism with consequent morbidity raises questions about the real benefit of unilateral adrenalectomy [63], considering that autonomous cortisol secretion is correlated with higher cardiovascular risk [64, 65].

Tanno et al demonstrated the benefits of sparing surgery in the treatment of PMAH [39]. This technique involves total adrenalectomy of the largest adrenal gland (usually the largest size and/or higher standardized uptake value on PET-FDG-CT) and partial adrenalectomy of the contralateral gland [37]. The potential benefit of subtotal adrenalectomy is to simultaneously enable the control of hypercortisolism and the preservation of adrenal function, considering the high morbidity and mortality associated with adrenal insufficiency [66]. With a follow-up of approximately more than 3 years, all patients recovered the adrenal axis with normalized 1 mg overnight dexamethasone suppression test [39].

Medical Treatment

The use of specific aberrant hormonal receptor antagonists is still proposed by some authors with the aim of limiting hypercortisolism in PMAH. However, reports of long-term success of this form of treatment are very rare [67, 68].

Because steroidogenesis in PMAH is inefficient, prescription drugs that inhibit adrenal cortisol synthesis may be helpful. Different treatments with ketoconazole [69, 70], metyrapone [71], mitotane [72], trilostane [73], and mifepristone [74] have been described with promising results. These medicines were prescribed primarily for patients who have contraindications to adrenalectomy or to improve presurgical clinical conditions. However, taking these medications can put patients at risk for side effects [75].

Conclusion

PMAH is a heterogenous and subdiagnosis adrenal disorder, and it is more genetically associated than previously thought. Therefore, advancements in genetic research are critical for improving diagnosis susceptibility and management for both index cases and their relatives, including other extra-adrenal disorders.

Acknowledgments

We would like to thank the full-time professors of São Paulo University, Department of Discipline of Endocrinology and Metabolism, Berenice Mendonça and Ana Claudia Latronico; and all collaborating fellows over the past 16 years: Marcia
Figure 3. Imaging of 1 patient with familial PMAH, ARMC5-positive. (A) Abdominal CT image (precontrast phase) with nodules with over 20 HU. (B) Imaging of 18F-FDG-PET/CT, showing bilateral adrenal nodules with 18F-FDG standardized uptake higher than that in the liver. SUVmax was elevated in these adrenal masses, reaching levels (arrows) frequently observed in malignant and metastatic lesions (SUVmax > 3.1). Source: Primary macronodular adrenal hyperplasia patient archive at the HCFMUSP Suprarenal Unit.

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Disclosures
The authors have nothing to disclose.

Data Availability
Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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