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COMMENT

Adrenal sparing surgery for lateralized primary aldosteronism: bringing it into the limelight?

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Primary aldosteronism (PA) is a prevalent endocrine hypertension associated with cerebro- and cardiovascular complications. The two most common subtypes are unilateral (lateralized) PA, mostly due to aldosterone-producing adenomas, and bilateral PA, due to diverse aldosterone-producing lesions. The former is a surgically curable form of hypertension caused by a unilateral adrenalectomy, whereas the latter is treated with mineralocorticoid receptor antagonists. Partial adrenalectomy (PADX) for unilateral PA is controversial, and no clear recommendations have been established [1]. While certain reports suggest PADX achieves high biochemical remission rates and preserves adrenal function [2–4], recent advancements in pathological diagnostic techniques, the combination of conventional hematoxylin and eosin (HE) staining and CYP11B2 immunohistochemistry, have improved the detection of aldosterone-producing lesions such as aldosterone-producing micronodule (APM) and their multiple forms (multiple aldosterone-producing micronodules[mAPM]/multiple aldosterone-producing nodules[mAPN]), which are morphologically indistinguishable from adjacent adrenal cortical cells using HE staining (HISTALDO criteria) [5]. Several studies reported that PADX targeting lesions visible on imaging or gross inspection may leave behind aldosterone-producing tissues in the residual adrenal gland, resulting in suboptimal therapeutic outcomes [6–8].

In this large-scale TAIPAI study, the authors analyzed data from 445 patients with unilateral PA with an image-identifiable adrenal nodule/adenoma who underwent total adrenalectomy based on the diagnosis of adrenal vein sampling (AVS) [9]. The resected adrenal glands were systematically categorized into three groups based on the HISTALDO criteria. This study focused on classical CYP11B2-positive APA/APN with or without accompanying mAPM/mAPN ("Black" and "Grey" groups) and significantly expanded the scope by including non-classical (CYP11B2-negative) non-functional tumors with accompanying mAPM/mAPN ("White" group) in their statistical analysis. They showed that the "Grey and White" groups, which included mAPM/mAPN, accounted for over 60% (Grey: 38.54%, White: 30.73%) of unilateral patients with PA, indirectly demonstrating that PADX targeting only tumors or nodules visible on imaging is insufficient to cure unilateral PA. Validating whether CYP11B2 immunohistochemistry in partially resected adrenals is consistent with clinical and biochemical outcomes in future studies is crucial (Fig. 1).

The authors demonstrated that the "Grey and White" groups had significantly lower complete remission rates and higher partial remission rates compared to the "Black" group with solitary APA/APN. Furthermore, a comparison between the "Grey" and "White" groups revealed that the "White" group had an even lower complete remission rate and a higher partial remission rate. These findings suggest the possibility of residual aldosterone-producing lesions in the contralateral adrenal gland, supporting the hypothesis that patients with a high burden of mAPM/mAPN in adrenalectomized specimens may have mAPM/mAPN in the contralateral adrenal gland [7]. Bilateral PA has traditionally been attributed primarily to adrenal hyperplasia; however, few studies have examined this assumption pathologically. Omata et al. reported that the primary cause of idiopathic hyperaldosteronism might not be hyperplasia but microaldosterone-producing adenomas or aldosterone-producing cell clusters [10]. Although this study focused on unilateral PA diagnosed using AVS with image-detectable

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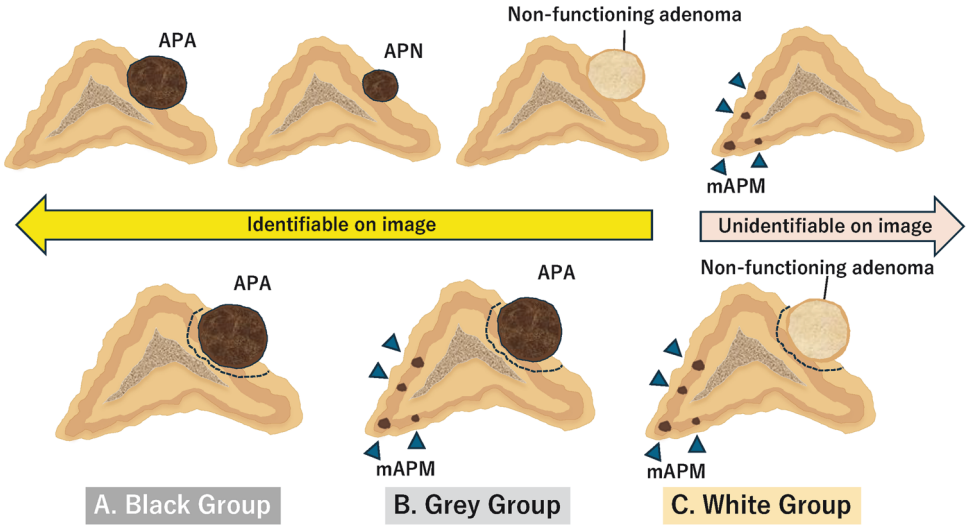

Fig. 1 Possible Subtypes of Lateralized Primary Aldosteronism According to Pathological Classification. The upper panel illustrates classification based on pathological findings. The first three categories (from the left) were identifiable on imaging, whereas the rightmost category was not. The lower panel shows the practical combinations of lesions observed in this study, categorized into black, gray, and white groups. APA aldosterone-producing adenoma; APN aldosterone-producing nodule; mAPM multiple aldosterone-producing micronodules

adrenal tumors, the results suggest that bilateral PA caused by bilateral mAPM/mAPN may be more common than previously anticipated.

Moreover, whether the current AVS criteria for lateralization diagnosis can be applied without modification in patients with PA and mAPM/mAPN remains debatable. The authors argued for the validity of these criteria (lateralized ratio [LR] > 2 without ACTH stimulation) for lateralization diagnosis because of high biochemical remission rates (80–90%) following total adrenalectomy in all three groups. However, 80–90% of the biochemical remission rates are insufficient. Furthermore, the AVS criteria vary significantly by country and institution. For instance, the Japan Endocrine Society recommends the criteria of LR ≥ 4 after ACTH simulation in combination with a contralateral ratio <1 [7]. Further investigations are needed to clarify how mAPM/mAPN responds to ACTH stimulation and whether residual mAPM/mAPN in the contralateral adrenal gland can be effectively excluded through contralateral suppression via AVS.

The authors noted the limitations of super selective AVS (SSAVS) in detecting mAPM/mAPN. While SSAVS aims to identify aldosterone-producing lesions by sampling branches perfusing the adrenal gland, it is challenging to accurately identify mAPMs/mAPNs that are undetectable via imaging or gross inspection and to determine the precise resection range. Additionally, PADX may be technically challenging in patients with multiple lesions, such as those in the grey group. However, as the authors stated, SSAVS might enable the identification of patients in the black group (solitary APA or dominant APN), leaving the potential for PADX as an applicable option.

In conclusion, this study highlights the diverse and complex nature of unilateral PA and emphasizes the importance of total adrenalectomy, not PADX, for optimal treatment outcomes. Future diagnostic and surgical strategies should integrate these findings to improve patient care.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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