Clinicopathologic Correlates of Primary Aldosteronism

Kai Duan, MD; Ozgur Mete, MD

- Primary aldosteronism is the most common cause of secondary hypertension, incurring significant cardiovascular morbidity and mortality. Our understanding of this disease has evolved substantially during the past decade. Recently, the molecular basis of primary aldosteronism has begun to be unraveled, with the discovery of mutations in potassium channel (KCNJ5), ATPases (ATP1A1, ATP2B3), and calcium channel (CACNA1D), and aberrant Wnt/β-catenin signaling. The most recent data suggest that 95% of cases are sporadic, whereas 5% of cases are hereditary. Pathologic correlates of primary aldosteronism include adrenal cortical hyperplasia, adenoma, and carcinoma. Although the most common clinical presentation is bilateral adrenal cortical hyperplasia, this entity is usually treated medically. Therefore, in the setting of primary aldosteronism, surgical pathologists are most commonly exposed to adrenocortical adenomas and the odd occasional carcinoma. This review provides an update on the current knowledge of primary aldosteronism and discusses the clinicopathologic correlations of this important disease.


First described by Conn in 1955, primary aldosteronism is defined as a group of disorders in which aldosterone production is inappropriately elevated, relatively independent from the renin-angiotensin system, and nonsuppressible by sodium loading.1–4 Our understanding of this disease has evolved drastically in the last decade with the advent of biochemical screening using plasma aldosterone to renin ratio (ARR).1–7 Previously thought to be a rare and relatively benign cause of hypertension, primary aldosteronism is currently recognized as the leading cause of secondary hypertension, with a prevalence of 5% to 13% among hypertensive adults.1–5 Furthermore, it incurs significant cardiovascular morbidity and mortality, which are specific to aldosterone itself.1–5 Pathologic correlates of primary aldosteronism include adrenal cortical hyperplasia, adenoma, and carcinoma. The diagnostic features of these entities have been refined during the past decade with the advent of modern imaging, biochemical testing, and molecular pathology.5–10 Primary aldosteronism is now known to comprise both sporadic (95%) and familial (5%) forms.11 Bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) accounts for 65% of sporadic cases of primary aldosteronism.1–4 With the advent of adrenal vein sampling, these lesions are almost never encountered in surgical pathology, because virtually all of the cases are treated medically.12,13 Rare cases of unilateral adrenal hyperplasia causing primary aldosteronism (2%) have been reported to benefit from surgical treatment1–4,7; however, the spectrum of morphologic changes in this context has not been extensively described. Aldosterone-producing adrenal cortical adenoma accounts for the remaining 30% of sporadic cases6–7 and is the most commonly encountered aldosterone-producing lesion in surgical pathology practice. Adrenocortical carcinoma has also been reported in 1% of cases of sporadic primary aldosteronism.1–7

CLINICAL AND LABORATORY FEATURES

In clinical practice, primary aldosteronism is equally reported in both sexes, with a peak incidence between ages 30 and 60 years; it is rarely seen in children.1–4 Normokalemic hypertension is the most common presentation, with hypokalemia present only in severe cases.1–5 Unlike patients with Cushing syndrome or adrenogenital syndrome, most patients with primary aldosteronism are usually asymptomatic and do not harbor any specific physical findings.1–5 Occasionally, some patients with marked hypokalemia may have symptoms such as muscle weakness and cramping, headaches, palpitations, polydipsia, polyuria, nocturia, or a combination of these.1–4 Primary aldosteronism is a laboratory diagnosis. The vast majority of cases are detected during routine biochemical screening of population groups with higher reported rates of primary aldosteronism.1,2 These include patients with refractory hypertension, hypokalemia, suggestive family history, or an incidentally detected adrenal mass.1–5 The current gold standard screening test is the plasma ARR.1–5 The most commonly adopted cutoff value of ARR is 30 ng/dL per ng/mL per hour (or 750 pmol/L per ng/mL per hour).1 When the ARR value is higher than the cutoff, the diagnosis of primary aldosteronism is confirmed or excluded by an aldosterone suppression test. The most widely used confirmatory tests are intravenous saline loading, oral sodium loading, fludrocortisone suppression, and captopril challenge test.1–5 Occasionally, primary aldosteronism is diagnosed as part of the workup for an incidentaloma, in which case special attention should be given to the biochemical results of an overnight
dexamethasone suppression test and 24-hour urinary measurement of fractionated metanephrines and catecholamines, to exclude Cushing or subclinical Cushing syndrome and pheochromocytoma.

In sporadic primary aldosteronism, some clinical and laboratory features are distinctive of hyperplasia (idiopathic hyperaldosteronism), adenoma, or carcinoma. Primary aldosteronism caused by adrenal cortical hyperplasia usually presents in older individuals, has a predominance among males, is more often normokalemic, and has less severe hypertension. By contrast, aldosterone-producing adenomas usually appear at an earlier age, occur more often in females, and are more often associated with hypokalemia and severe hypertension. When primary aldosteronism is caused by an adrenocortical carcinoma, it usually presents with much more profound hypokalemia, very high aldosterone concentrations, and in some cases concurrent cortisol and/or sex-steroid production, leading to Cushing syndrome or virilization.

Three types of familial primary aldosteronism have also been identified—all are inherited in an autosomal-dominant manner (Table).

Familial hyperaldosteronism type I, also known as glucocorticoid-remediable aldosteronism, has been attributed to less than 1% of cases of primary aldosteronism and is caused by a recombination between the CYP11B2 and CYP11B1 genes. Familial hyperaldosteronism type II is responsible for 3% to 5% of cases of primary aldosteronism and has been linked to 7p22, although no specific gene has been identified to date. Familial hyperaldosteronism type III is a more recent discovery and has been found in less than 1% of cases, involving mutations in a potassium channel (KCNJ5).

Hereditary forms of primary aldosteronism typically manifest more florid symptoms, with the exception of familial hyperaldosteronism type II, which is clinically and biochemically indistinguishable from sporadic cases. Familial hyperaldosteronism type II is usually only diagnosed when at least two first-degree members of the same family have confirmed primary aldosteronism and after familial hyperaldosteronism types I and III have been excluded. Most individuals with familial hyperaldosteronism type I develop severe hypertension early in life (before the age of 20 years) and display high rates of morbidity and mortality from cerebrovascular events, although milder clinical phenotypes have also been reported. A defining feature of familial hyperaldosteronism type I is that administration of exogenous glucocorticoids reverses the state of mineralocorticoid excess. Individuals with familial hyperaldosteronism type III typically develop an early-onset and particularly severe form of primary aldosteronism, with very high aldosterone concentrations (2–10 times normal concentrations), marked hypokalemia, and severe hypertension resistant to medical therapy.

### RADIOLOGIC FEATURES

Once primary aldosteronism is confirmed biochemically, radiologic investigations provide a preliminary method for localization and subtyping of aldosterone-producing lesions. Adrenal computed tomography (CT) scan is the initial modality of choice. The findings on CT for adrenal hyperplasia are usually nonspecific, showing either enlarged or normal-size adrenal glands. Adrenal adenomas usually appear homogeneous, round, and small, with smooth borders and well-delineated margins (Figure 1, A). Radiologic features of tumors suspicious for adrenocortical carcinoma include larger size (>4 cm), irregular margins, inhomogeneous contents, and areas of necrosis, hemorrhage, and calcification. Because of the fact that adenomas often have intracytoplasmatic fat, resulting in lower attenuation, measurement of the attenuation value in Hounsfield units is helpful in distinguishing adenomas from nonadenomas; tumors with attenuation values of less than 10 Hounsfield units on an unenhanced CT are often diagnostic of adrenocortical adenomas (Figure 1, A). It is important to note, however, that CT cannot reliably visualize microadenomas or hyperplasia, or determine the functional status of an adrenal cortical adenoma.

Given the limitations of adrenal CT scan, adrenal venous sampling has become the gold standard test to determine lateralization of the source of the excessive aldosterone secretion. This method is also helpful in differentiating aldosterone-producing adenoma from bilateral adrenal hyperplasia. After successful catheterization of both adrenal veins under interventional radiology, comparison of the aldosterone to cortisol ratio between both sides is the currently accepted criterion for determining unilateral versus bilateral disease. This is also known as the lateralization index (aldosterone-to-cortisol ratio on the dominant side divided by the aldosterone-to-cortisol ratio on the non-dominant side). Most investigators concur that a lateralization index of 4 or higher during cosyntropin stimulation (≥2 for unstimulated adrenal vein sampling) is indicative of unilateral aldosterone production and favors the diagnosis of aldosterone-producing adenoma, whereas a lateralization index lower than 4 is more suggestive of bilateral adrenal hyperplasia.

<table>
<thead>
<tr>
<th>FH Type</th>
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<th>Clinical Features</th>
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<tr>
<td>FH-I</td>
<td>Autosomal dominant</td>
<td>CYP11B1, CYP11B2</td>
<td>Early onset (often before age 20 y), resistant hypertension, mostly normokalemic, complete aldosterone response to dexamethasone</td>
<td>Normal adrenal glands; occasional adrenal cortical nodular disease or bilateral hyperplasia</td>
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<td>FH-II</td>
<td>Autosomal dominant; undetermined in some cases</td>
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<td>Clinical features indistinguishable from sporadic primary aldosteronism: onset in adulthood, resistant hypertension, mostly normokalemic</td>
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<td>Very early onset (childhood), severely resistant hypertension, hypokalemia, very high aldosterone concentrations (2–10 times normal concentrations)</td>
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*Data derived from Bar-lev and Annes, Zennaro et al, Scholl and Lifton, and Mulatero et al.*

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**Overview of Familial Hyperaldosteronism (FH)**

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**Table of Familial Hyperaldosteronism Types**

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Figure 1. Characteristics of aldosterone-producing adrenal cortical adenomas. Computed tomography (CT) scan identified a solitary, round, well-circumscribed lesion with an attenuation value of less than 10 Hounsfield units on an unenhanced CT in a patient with primary aldosteronism (A). From a radiologic perspective, the findings were consistent with an adrenal cortical adenoma. Gross examination justified the presence of a well-defined mass showing a golden yellow appearance (B). The lesion did not show evidence of malignancy and consists of clear cells (C). The nontumorous adrenal cortex is not atrophic (B and C) but shows zona glomerulosa layer hyperplasia (arrows) characterized by a continuous and multilayered zona glomerulosa layer (D). The overall findings are diagnostic of an aldosterone-producing adrenal cortical adenoma (B through D). The presence of spironolactone bodies within an adrenal cortical adenoma provides another morphologic clue leading to recognition of aldosterone production if the patient is treated with spironolactone (E). The distinctive feature of spironolactone bodies is their concentric and lamellated patterns (E). Luxol fast blue stain can be used to distinguish these inclusions from other mimics because of their rich content of phospholipids (F) (hematoxylin-eosin, original magnifications ×1.25 [C], ×10 [D], and ×20 [E]; Luxol fast blue, original magnification ×20 [F]).
aldosterone production involving bilateral adrenal hyperplasia.17

**GROSS FEATURES**

The normal adult adrenal gland weighs 4 g at surgical excision,12,13,16 with an average cortical thickness of almost 2 mm.12 However, there may be variation from gland to gland or thicker areas in different parts of the same gland.12 Grossly, adrenal gland with hyperplasia (idiopathic hyperaldosteronism) may appear unremarkable or show slight enlargement, with grossly visible micronodules or macro nodules.12,13 Aldosterone-producing adenomas often present with a round-to-ovoid unicentric neoplasm measuring a few centimeters in diameter.12,13,15,16,19 Most adenomas are unilateral and solitary, but occasional bilateral adenomas have also been reported.13,16,19 These tumors are often intra adrenal and unencapsulated, but some may also show a true capsule or a pseudocapsule.12,15,16 The cut surface is classically described as homogenous, and golden yellow or “canyon yellow” (Figure 1, B), and larger tumors may have areas of hemorrhage or cystic change.12,13,15,16,19 Adrenocortical carcinomas usually weigh more than 100 g, and can measure from 3 to 40 cm15,16, some are encapsulated, but many are adherent to or invade adjacent structures.15,16 On slicing, they often show lobulation with fibrous bands and areas of necrosis and hemorrhage.15,16

The gross features of familial hyperaldosteronism are scarcely reported in the literature. In type I, macroscopic examination usually reveals normal adrenal glands, although some cases showing adrenal cortical nodular disease and massive bilateral adrenal hyperplasia have been described.11,20 In type II, gross examination can reveal either adrenal cortical adenoma or bilateral hyperplasia.11 In type III, the adrenal glands show marked bilateral hyperplasia, which can be seen grossly, although normal adrenal glands have also been described in some families.11

During the gross examination, particular attention should be given to the width of the cortex.13,15,19,24 Even grossly, the identification of atrophy of the nontumorous adrenal cortex in a gland with a dominant cortical adenoma should prompt the attention of the surgical pathologist to determine whether the patient has been diagnosed with concurrent Cushing syndrome. If not, a timely call to the treating physician will prevent the unanticipated postoperative crisis of acute Addison disease.21

**HISTOPATHOLOGIC FEATURES**

The histopathologic correlates of primary aldosteronism include adrenal cortical hyperplasia, adenoma, and carcinoma. Although adrenal cortical hyperplasia is the most common clinical presentation, this entity rarely presents itself in surgical pathology, because most cases involve bilateral glands and are treated medically.12,13 Although rare examples of unilateral adrenal cortical hyperplasia have been reported in patients with primary aldosteronism, the spectrum of morphologic changes has not been extensively defined in this setting.1,2,12,13 Therefore, with the exception of paradoxical zona glomerulosa (ZG) hyperplasia, pathologists are most commonly exposed to adrenal cortical neoplasms, especially adenomas, from patients with primary aldosteronism.12,13,15,16,19

On light microscopy, aldosterone-producing adrenal cortical adenomas appear partially or completely encapsulated, with a compressed fibrous rim or fibrous “pseudo capsule” at the expansile borders of the tumor (Figure 1, C).12,15,16 Tumor cells often present in a nesting or alveolar pattern, as short cords, as blunt anastomosing trabeculae, or as mixtures of these architectural patterns.12 The morphologic characteristics of individual cells may be quite heterogeneous, with varying proportions of 4 different types of cells: clear cells resembling zona fasciculata cells, cells resembling ZG cells, compact cells indistinguishable from those of the zona reticularis, and a group of cells designated as “hybrid” cells with cytologic features of both zona fasciculata and ZG cells.12,13,15,18–25 Lipid-rich clear cells usually predominate in these lesions, giving them a characteristic golden yellow color.12,15,19,21,22 Similar to other endocrine lesions, oncotic change has also been reported in the literature.12,22 Some cases exhibit cytoplasmic eosinophilic globular inclusions, reflecting degenerated mitochondria.22

Occasionally, the existence of a cortisol-producing adenoma may be missed by the clinician preoperatively. Although this may be due to an omission, a variant of aldosterone-producing adenoma with concurrent cortisol production has also been described.23 The distinction between cortisol-producing adenoma and aldosterone-producing adenoma can be made on hematoxylin–eosin–stained slides by assessing the nontumorous adrenal cortex.12,21,22 Cortisol-producing adrenal cortical adenomas are associated with atrophy of the nontumorous cortex due to the negative feedback suppression effect of the hypothalamic–pituitary axis.12,13,21,22

Unlike glucocorticoid-producing adenomas, aldosterone-producing cortical neoplasms are not associated with cortical atrophy,12,13,15,18–22 and paradoxical ZG hyperplasia can be identified in the nontumorous adrenal cortex (Figure 1, D).12,13,15,19–22 The ZG is composed of small angular cells with a high nuclear to cytoplasm ratio, dispersed focally below the capsule. In other words, the presence of a continuous ZG layer is a sign of hyperplasia. The presence of spironolactone bodies within an adrenal cortical adenoma provides another morphologic clue leading to recognition of aldosterone production.12,13,15,19–22 These are described as intracytoplasmic eosinophilic inclusions following spironolactone treatment (Figure 1, E).12,13,15,19–22 These inclusions are often small (2–12 μm), round to oval, and delineated from surrounding cytoplasm by a small, clear halo.12 Red blood cells and other intracytoplasmic inclusions can sometimes mimic spironolactone bodies. Although a distinctive feature of spironolactone bodies is their concentric and lamellated pattern, Luxol fast blue stain can also be used to distinguish these inclusions from other mimickers because of their rich content of phospholipids (Figure 1, F).12

Despite being a rare cause of primary aldosteronism, adrenocortical carcinoma must be excluded, particularly if a large tumor is found.1,4,12,13,15,19 Histologic examination reveals a more disorganized architecture than in adenomas, with trabecular and diffuse patterns.12,13,15,19,24 Nuclear pleomorphism and increased mitoses (>5 per 50 high-power fields), including atypical figures, are often present, along with capsular and/or vascular invasion in the vast majority of high-grade adrenocortical carcinomas.12,13,15,19,24 However, making the distinction between a noninvasive low-grade adrenocortical carcinoma and adrenal cortical adenoma with atypical features can be challenging. Although many scoring schemes have been defined in this field, even the most commonly used Weiss scoring scheme carries significant interobserver variability, along with a gray zone when an adrenal cortical neoplasm receives a score of
ANCILLARY STUDIES

The ultrastructural features of aldosterone-producing adenomas are unique. Aldosterone-producing cells contain mitochondria with lamella-type or platelet cristae, characteristic of ZG-type cells, whereas glucocorticoid-producing and nonfunctioning adenoma cells contain mitochondria with tubulovesicular cristae.12,13,21,22 Furthermore, ultrastructural spironolactone bodies, consisting of a central core with amorphous, electron-dense material surrounded by multiple concentric membranes, are seen in aldosterone-producing adenoma.12,13,21,22

Currently, immunohistochemical tests are not part of the routine histopathologic assessment of aldosterone-producing lesions, because most cases can be given a diagnosis using conventional histology in conjunction with biochemical evidence of primary aldosteronism.12,13,15,19–22 In the past, some investigators have used positive P450(c17) and 3β-hydroxysteroid dehydrogenase immunostaining as evidence of steroid production in aldosterone-producing cells, although these also stain positive in cortisol-producing cells.13,27,28 Recently, two studies concurrently described the use of a novel immunostain, CYP11B2, to confirm the production of aldosterone and the histopathologic diagnosis of primary aldosteronism.27,28 CYP11B2 is a key enzyme for aldosterone synthesis, and positive staining for CYP11B2 is indicative of cells producing aldosterone in both tumor and in the ZG of adjacent tissue.27,28 Occasionally, when there is a need to distinguish an adrenal cortical adenoma from another tumor, one can confirm the adrenal cortical origin by demonstrating positivity for universal markers of adrenal cortical cytodifferentiation, including steroidogenic factor-1, Melan-A (clone A103), calretinin, synaptophysin, and α-inhibin.

PATHOGENESIS AND MOLECULAR BIOLOGIC FEATURES

In normal physiology, aldosterone is secreted by the adrenal cortex in response to hyperkalemia and angiotensin II.6,8–10 The responsive cells are typically hyperpolarized because of predominant K+ conductance, which is primarily mediated by K+ channels (A). Activation of the renin-angiotensin system leads to production of angiotensin II (AT2), which binds to type 1 angiotensin II receptor (AT2R) on the zona glomerulosa cells, inhibiting potassium currents and inducing cell membrane depolarization. This depolarization activates voltage-gated Ca2+ channels: the influx of calcium and the activation of the calcium/calcmodulin kinase pathway result in aldosterone synthesis (B). In primary aldosteronism, sporadic mutations arising in potassium channels (KCNS5), calcium channels (CACNA1D), and ATPases (ATP1A1 and ATP2B3) account for approximately 60% of aldosterone-producing adenomas (C). Mutations in the KCNS5 gene result in sodium permeability of the mutant K+ channel, causing cellular depolarization and subsequent calcium influx. In other cases, mutations in the ATP1A1 gene lead to loss of Na+/K+ ATPase pump activity, resulting in cell membrane depolarization. Deletions in the ATP2B3 gene, encoding Ca2+ ATPase, result in distorsion of the Ca2+-binding site and affect intracellular calcium clearance. Somatic mutations in the CACNA1D gene, which encodes the voltage-gated Ca2+ channel, cause channel activation at less depolarized potentials.

2 or 3. Recently, Volante et al25 introduced a simplified approach by using the “reticulain algorithm” to define malignancy through an altered reticulin network associated with one of the following parameters: high mitotic rate (>5 mitoses per 50 high-power fields), vascular invasion, and necrosis. This method has subsequently been shown to have a high interobserver reproducibility.26 Furthermore, insulin-like growth factor 2 and p53 overexpression, and a high amount of Ki-67 (>5%) have also been shown to be effective in differentiating carcinoma from adenoma.15,16,24
Although the causal gene underlying type II familial hyperaldosteronism has not yet been identified, some reports have linked it to chromosome 7p22.5,6,8,10,11

During the past 2 years, considerable interest has been generated by the discovery of sporadic mutations in potassium channels (KCNJ5), calcium channels (CACNA1D), and ATPases (ATP1A1 and ATP2B3; Figure 2, C). Together, these 4 mutations account for approximately 60% of aldosterone-producing adenomas.25–33 KCNJ5 encodes Kir3.4, an inward rectifier potassium channel in ZG layer cells.30 Two common somatic gain-of-function mutations (G151R and L168R) located in or close to the selectivity filter have been reported in 40% of aldosterone-producing adenomas.8–11 The mechanism underlying aldosterone production and cell proliferation is the sodium permeability of the mutant KCNJ5 channel, causing cellular depolarization and calcium influx through voltage-gated calcium channels.8–11 Recently, a lower expression of the KCNK5 gene encoding Twik-related Acid-sensitive K+ channels 2 (TASK2) has also been described in aldosterone-producing adenomas and was shown to increase production of aldosterone in vitro.30 Some investigators suggested that KCNJ5 mutations are more prevalent in aldosterone-producing adenomas resembling clear cells of the zona fasciculata but are absent in a subset of aldosterone-producing adenomas resembling small angular cells of the ZG cells.30 Exon sequencing of the latter group identified somatic mutations in either ATP1A1 or CACNA1D, which could suggest a common subtype of aldosterone-producing adenoma.30 Many adenomas harboring these mutations were less than 1 cm in diameter and had been overlooked on conventional adrenal imaging.30,31

ATP1A1 (encoding Na+/K+ ATPase α subunit) and ATP2B3 (encoding Ca2+/ATPase) play an important role in the regulation of aldosterone production by maintaining cell membrane potential.30,31 Mutations in the Na+/K+ ATPase α subunit lead to a loss of pump activity and reduced affinity for K+ (Figure 2, C).30,31 Deletions in ATP2B3 are inferred to cause distortion of the Ca2+-binding site and to affect intracellular calcium clearance (Figure 2, C).30,31 Another study identified somatic mutations (Gly403 and Ile770) in the CACNA1D gene, which encodes a voltage-gated calcium channel (Ca1.3; Figure 2, C).30,32 The altered residues cause channel activation at less depolarized potentials. G403 alterations also impair channel inactivation.30,32 These effects are inferred to cause increased Ca2+ influx, which in turn stimulates aldosterone production and cell proliferation.30,32

In the adrenal gland, dysregulation of the Wnt/β-catenin signaling pathways has already been reported in the development of micronodular and macronodular hyperplasia and adrenocortical neoplasms.24,30,33 Recently, a study has shown that Wnt/β-catenin signaling is aberrantly activated in 70% of aldosterone-producing adenomas in a series of 47 patients.34 This study also provides further evidence that decreased expression of the Wnt inhibitor SFRP2 may be contributing to dysregulated Wnt signaling and aldosterone-producing adenoma development in some patients.34

TREATMENT AND PROGNOSIS

Unilateral laparoscopic adrenalectomy is currently the gold standard for treatment of aldosterone-producing adenomas and often results in improved blood pressure and serum concentrations postoperatively.1–5 In bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), the preferred treatment is usually pharmacologic, using mineralocorticoid antagonists.1–4 Although spironolactone is still recommended as the primary agent, eplerenone has been described as an alternative option.3 In rare cases of unilateral adrenal hyperplasia, unilateral adrenalectomy has been shown to be beneficial, although the long-term outcome of surgery has not been extensively reported.1–3 Aldosterone-producing adrenocortical carcinoma is treated similarly to other adrenocortical carcinomas, with surgical resection and adjuvant mitotane treatment.3,5 The guidelines for the testing of familial hyperaldosteronism have not been firmly established.1–7,31 Currently, only screening for familial hyperaldosteronism type I has been recommended in patients with early onset of primary aldosteronism and those with a family history of primary aldosteronism or stroke at a young age.1 The initial treatment for familial hyperaldosteronism type I consists of low-dose dexamethasone; spironolactone or amiloride may also be considered if treatment with glucocorticoid does not normalize blood pressure.1–4

CONCLUSION

Despite emerging evidence using genomic sequencing, there is still much debate regarding the molecular mechanisms leading to hyperaldosteronism, cell proliferation, and tumor formation. Pathologic correlates of primary aldosteronism include adrenal cortical hyperplasia, adenoma, and carcinoma. Although each aldosterone-producing lesion possesses particular clinical, laboratory, and radiologic findings, preoperative subtyping may be difficult in some cases. Therefore, it is important for the practicing pathologist to recognize the spectrum of primary aldosteronism and differentiate aldosterone-producing adrenal cortical adenoma from hyperplasia and carcinoma, because it is of tremendous importance for management.

References