Case Report

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A Case of ACTH Independent Macronodular Adrenocortical Hyperplasia Presenting with Conns Syndrome

Neethika Menon*, Anitha Padmanabhan, Nithin M Gadgil, Milind.V.Patil

Department of Pathology, Lokmanya Tilak Municipal Medical College, Sion, Mumbai

Abstract

Backgound: ACTH Independent macronodular adrenocortical hyperplasia (AIMAH)is a rare cause of hyperaldosteronism and is characterised by bilateral adrenal hyperplasia . One of the most common presenting symptoms is refractory hypertension. Clinical features and hypertension usually resolve following adrenalectomy. Timely diagnosis of such conditions are pertinent as they are completely treatable and thus prevents further comorbidities associated with hypertension and hypokalemia like arrhythmia.

Case Presentation: A 57 year old male patient presented with unresolved hypertension since 15 years even after treatment with three different antihypertensives drugs since last one year. He was detected with raised serum aldosterone levels. Adrenal venous sampling showed lateralisation to the left adrenal. CT abdomen and pelvis revealed enlarged and nodular left adrenal gland and a bulky right adrenal gland. Laparoscopic left adrenalectomy was performed. Grossly left adrenal showed multiple well circumscribed yellow coloured nodules restricted to the cortex. Microscopy showed multiple well circumscribed unencapsulated nodules comprising of compact cells with clear to vacuolated cytoplasm and round central nucleus along with few foci of myelometaplasia.

Conclusion: Conns syndrome causes a high rate of mortality and morbidity of left untreated. Serum aldosterone, serum cortisol and serum electrolyte levels should be carried out in every case of refractory hypertension to rule out adrenocortical lesions. Timely diagnosis goes a long way in reducing morbidities associated with hypertension and dyselectrolytemia.

Keywords: *Adenoma, Hyperplasia, Conns syndrome, Adrenal, Aldosterone*

Introduction

ACTH independent macronodular hyperplasia is a rare cause of Conns syndrome. Hyperplasia of the adrenal cortex is virtually always bilateral. It is a rare disorder and occurs in less than 1% of cases with Cushing's syndrome. Nodular hyperplasia is divided into micronodular (<0.5cm)and macronodular types(>0.5cm) based upon the size of the nodules(1). With the sensitive imaging of computerized tomography (CT) and magnetic resonance imaging (MRI), adrenal cortical nodules less than 1.0 cm in size can be detected. Careful gross dissection of the adrenal glands with removal of all periadrenal connective tissue and fat with transverse sectioning at 3 mm interval may be necessary for the accurate determination of the size and weight of the gland since the changes could be subtle. Primary hyperaldosteronism results from excessive secretion of aldosterone by the adrenal glands). Under normal conditions, the most important regulators of aldosterone secretion are the renin-angiotensin system and pottasium, apart from ACTH .

It has been estimated that 15 to 35 percent of cases of primary hyperaldosteronism are idiopathic, with bilateral hyperplasia of the zona glomerulosa. With increased awareness of milder forms of primary hyperaldosteronism , an incidence of 45 percent has been reported .In the idiopathic form, the clinical features are hypertension, headache, easy fatiguability, and weakness . Adrenal venous sampling is an essential diagnostic step in most patients with primary aldosteronism to distinguish between unilateral and bilateral adrenal aldosterone hypersecretion.(2)

Case Report

A 57 year old male patient came with a history of unresolved hypertension since the last 15 years. Since the last one year he has been on three different antihypertensive drugs. His blood investigations revealed serum cortisol levels of 12.5mcg/dl(5-25 mcg/dl) and serum aldosterone levels of 47.5ng/dl(2-9 ng/dl). Serum sodium 142 mEq/dl(135-145mEq/l), serum potassium 4.6 mEq/dl(3.5-5.5mEq/dl), serum calcium 9.7 mg/dl(9-11mg/dl) and serum

ACTH were within normal limits. Since his serum aldosterone levels were high, CT abdomen and pelvis was done which revealed mildly bulky left adrenal gland showing nodularity and a minimally bulky right adrenal gland(Fig 1).

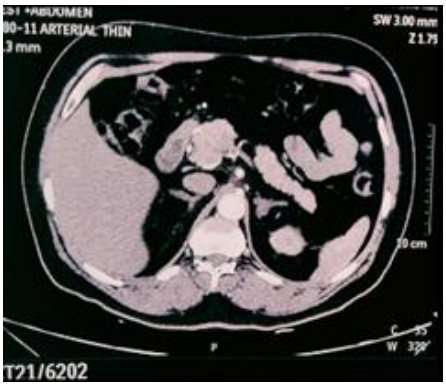

Figure 1: Abdominal computed tomography of our patient showing multinodular enlargement of left sided adrenal gland and minimally bulky right adrenal gland.

ACTH stimulation with lateralization was performed which showed lateralization to the left adrenal. The lateralization index was 4.88(<4) and contralateral suppression index was 0.16. Based on the radiological and laboratory findings a clinical diagnosis of primary hyperaldosteronism or conns syndrome was made. Laparoscopic left adrenalectomy was performed.

We received the left adrenal gland measuring 5.5*1.3*0.5cm. Four well circumscribed nodules were noted, yellow in color, largest measuring 1*1cm and smallest measuring 0.5*0.5cm. The nodules were restricted to the cortex and the surrounding adrenal cortex appeared unremarkable. There was no evidence of hemorrhage or necrosis and the adrenal medulla was grossly uninvolved (Fig 2).

Figure 2: Macroscopic appearance of left adrenal gland. The left adrenal gland is enlarged and shows a large well circumscribed and multiple small well circumscribed nodules restricted to the cortex.

Histopathology revealed multiple well circumscribed nodules, restricted to the adrenal cortex, comprising of large compact uniform cells with clear to vacuolated cytoplasm and small round nucleus(Fig 3). Few foci of myelolipoma Tous metaplasia were noted (Fig 4). Surrounding cortex showed unremarkable zona fasciculata and reticularis. There was no evidence of mitosis, invasion, hemorrhage or necrosis. The differentials considered were adrenocortical hyperplasia and adrenocortical adenoma. Since the nodules were unencapsulated and the adjacent cortex was unremarkable with no evidence of atrophy, the diagnosis was narrowed down to adrenocortical hyperplasia.

Post surgery, our patient was symptomatically better and is currently on a single anti-hypertensive drug.

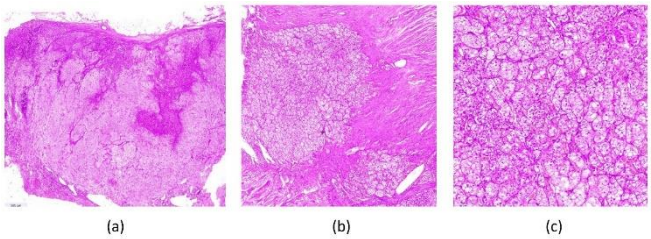

Figure 3: (a),(b) and (c) Microscopic examination of H and E((4x) ,(10x), (40x) respectively) stained sections shows a nodule confined to the adrenal cortex.(c) Microscopic examination of H and E (40x) stained sections show large compact uniform cells with clear to vacuolated cytoplasm and small round nucleus.

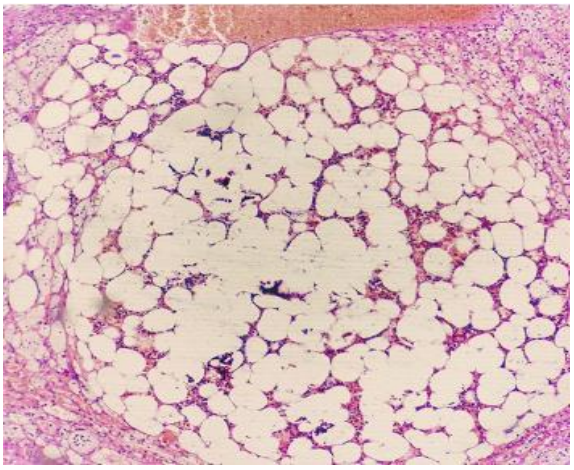

Figure 4: Microscopic examination of H and E(10x) stained sections show a focus of myelolipomatous metaplasia.

Discussion

Primary adrenocortical hyperplasia is also known as ACTH Independent macronodular adrenocortical hyperplasia (AIMAH). This usually presents as a bilateral adrenal mass with an age group of presentation between 20 to 60 years.

Two main causes of primary aldosteronism are adrenal adenoma and primary adrenal hyperplasia. Differentiating between these two causes is important because an

aldosterone-producing adenoma is usually best treated surgically, whereas bilateral adrenal hyperplasia is generally managed medically. Adrenocortical hyperplasia can be primary or secondary. Primary adrenocortical hyperplasia is nodular and can be due to conns syndrome (as in our case) or Cushing's syndrome. Secondary adrenocortical hyperplasia is usually diffuse And secondary to any pituitary disease or ectopic ACTH production. Tokumoto M et al described a similar case of a 56 year old hypertensive patient with elevated plasma aldosterone levels , low plasma ACTH and bilateral adrenal swelling. The diagnosis of adrenal hyperplasia was confirmed on morphology and positive immunostaining with adrenal synthetase(3)

The most common cause of AIMAH are activating mutations in ARMC5 (ACTH receptor mutation), MEN1, KCNJ5 mutation , PRKAR1 A(associated with primary pigmented nodular adrenocortical disease), carney s complex and mutations associated with FAP. Occasional association with McCune Albright syndrome and hereditary leiomyomatosus and renal cell cancer have been noted. Clinical features are usually associated with the underlying disease(conns syndrome or Cushing's syndrome. (1)Biochemical investigations reveal increased serum aldosterone levels(conns syndrome) as in our case or increased serum cortisol levels(Cushing's syndrome) along with low serum acth levels(primary), deranged serum pottasium and sodium levels. C T reveals enlarged adrenals with multiple nodules. CT is widely used to differentiate between the adrenal adenomas and primary adrenal hyperplasia .Until now, the diagnosis of bilateral adrenal hyperplasia has been made by excluding the presence of an adenoma on such imaging. According to R.K Lingam, no significant difference in the size of the body of the adrenal glands was detected between aldosterone-producing adenoma and bilateral adrenal hyperplasia. However, each adrenal limb was significantly larger in patients with bilateral adrenal hyperplasia than in those with aldosterone-producing adenoma.(4)

Adrenal venous sampling is done for lateralisation, which is used to determine the active nodule and plan further treatment. Grossly, the adrenals are enlarged and nodular in primary hyperplasia. Nodules can be micronodules or macronodules , occasionally showing pigmentation(primary pigmented nodular adrenocortical disease). Secondary hyperplasia is diffuse and more severe in cases of ectopic ACTH production than in pituitary diseases. Nodules are grossly undetectable when due to conns syndrome. Combination of nodular an diffuse types are also seen. Microscopically, adrenal cortex shows multinodular architecture as in our case or diffuse pattern. Cells are large, uniform in size, with vacuolated (conns syndrome)or eosinophilic granular cytoplasm(Cushing's syndrome) (5).Areas of lipomatous metaplasia were also noted in our case which is similar to a case reported by C Finch et al. His study also showed extensive lipomatous metaplasia in a case of bilateral macronodular adrenal hyperplasia . This distinctive change , according to him, is due to the metaplastic transformation of either stromal cells or adrenocortical cells(6).Zona glomerulosa hyperplasia as 5 cell thick nests in the periphery comprising of cells with scant eosinophilic cytoplasm can be seen. Pigmented nodules composed of large cortical cells with granular dark brown pigment can be seen in cases of PPNAD.

Main differential for adrenocortical hyperplasia is adrenocortical adenoma which can be distinguished by presence of capsule and atrophy of adjacent cortex.

Nodules in AIMAH stain positive for 3 betahydroxysteroid dehydrogenase.Special stains for the nodules in PPNAD are synaptophysin and 17 alpha hydroxylase cytochrome p450 . According to a study conducted by W.C McCluggage,monoclonal antibody against alpha inhibin stained zona reticularis of normal adrenal cortex. It also stained cells with eosinophilic cytoplasm which resembled the cells of zona reticularis,whereas staining was absent in cells with clear cytoplasm in cases of adrenal hyperplasia.All cases of adrenocortical carcinoma exhibited positive staining.(7) Most important consequence of primary aldosteronism secondary to adrenocortical lesions is end organ damage which includes end stage renal disease and irreversible cardiovascular damage. (8)

The latest treatment guidelines and protocols according to a study published by W.F Young et al, if the patient has bilateral adrenocortical masses and does not desire surgery or if patient has a unilateral mass and does not desire surgery or if there is no lateralisation with adrenal vein sampling,medical treatment with mineralocorticoid receptor antagonists can be done. If the patient has unilateral adrenocortical mass and has lateralisation with adrenal vein sampling and desires surgery, unilateral laparoscopic adrenalectomy can be done. (8).

Conclusion

We reported a rare case of AIMAH accompanied by primary hyperaldosteronism, which was confirmed by detailed histopathological examination. Early diagnosis of this condition is of utmost importance to avoid cardiovascular and renal complications and initiating timely and precise treatment modalities.

Abbreviations:

AIMAH: Aldosterone independent macronodular adrenocortical hyperplasia

PPNAD: Primary pigmented nodular adrenocortical disease

FAP: Familial adenomatous polyposis

ACTH: Adrenocorticotropic hormone

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Corresponding Author:

Dr.Neethika Menon

Email: neethu.8693@gmail.com

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