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Editorial

Complaisant and Amiable-Adrenocortical Adenoma

Anubha Bajaj*

Department of Histopathology, Panjab University/A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University/A.B. Diagnostics, India.

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Adrenocortical adenoma is a benign neoplasm arising from cells of adrenal cortex. Additionally designated as adrenal cortical adenoma (ACA), adrenocortical adenoma may or may not emerge as a functional neoplasm.

Besides, an incidentaloma or miniature adenoma may be discovered incidentally during imaging procedures for diverse lesions, black or pigmented adenoma demonstrates diffuse pigmentation or a brown-black adrenocortical adenoma appears imbued with lipofuscin.

Hypercortisolism or Cushing's syndrome may occur as

- Preclinical or subclinical Cushing's syndrome wherein hypercortisolism occurs within context of an incidental adrenal tumefaction in the absence of overt clinical manifestations
- Primary hypercortisolism occurs due to secretion of cortisol by adrenal gland
- Secondary hypercortisolism emerges due to enhanced secretion of adrenocorticotrophic hormone (ACTH) by pituitary gland or due to secretion of cortisol by an ectopic neoplasm.

Nevertheless, adrenal neoplasms with undetected clinical symptoms may not be contemplated as incidentalomas [1,2].

Adrenocortical adenoma commonly occurs in adults between fifth decade to seventh decade. Disease incidence increases with advancing age wherein lesions appear <1% in subjects < 30 years and ~7% in subjects > 70 years. Adrenocortical adenoma is uncommon in children. A bimodal age distribution is observed wherein the neoplasm is commonly discerned< 5 years and between 9 years to16 years.

An equivalent predilection for right and left adrenal glands is encountered. A female predominance is observed with female to male proportion of 1.6:1 [1,2].

Adrenocortical adenoma may be associated with specific mutation of p53 gene as R337H TP53 and several genetic syndromes as Beckwith- Wiedemann syndrome, Li-Fraumeni syndrome or sarcoma, breast, leukaemia and adrenal gland (SBLA) syndrome, Carney's triad or adrenogenital syndrome [2,3].

Of obscure tumorigenesis, appropriate diagnosis is pertinent to cogent immunohistochemistry. Adjunct molecular assessment for evaluating clinical, therapeutic and prognostic outcomes or for distinction from adrenocortical carcinoma remain undefined and unutilized [2,3]. Adrenocortical adenoma emerges as a monoclonal and diploid neoplasm, in contrast to monoclonal aneuploidy or polyploid adrenocortical carcinoma.

Generally sporadic, adrenocortical adenoma may be associated with a genetic syndrome.

Cortisol secreting adrenocortical adenoma may be associated with McCune-Albright syndrome manifesting as a primary pigmented nodular adrenocortical disease or Carney's complex.

Comparative genomic hybridization (CGH) evaluation exhibits adrenal tumours with complex chromosomal alterations wherein adrenocortical carcinoma demonstrates significant chromosomal gains or losses, in contrast to adrenocortical adenoma [2,3].

Single nucleotide polymorphism (SNP) array confirms preponderant genetic variability within adrenocortical adenoma. Chromosomes 2, 5, 3, 6 and 11 frequently demonstrate genomic gains. Chromosomes 1, 6, 2 delineate genomic losses. Candidate genes appear as NOTCH1, CYP11B2, HRAS or IGF2.

Gene expression profiling exemplifies decimated expression of major histocompatibility complex (MCH) class II genes within paediatric adrenocortical carcinoma, in contrast to adrenocortical adenoma.

Adrenocortical adenoma is configured from three layers of adrenal cortex although neoplasm may be ectopic and occur within sites such as gastric wall and spinal cord.

An estimated 90% of adrenocortical adenomas appear as non functional neoplasms [2,3].

Functional tumours may produce ≥one of predominant categories of adrenal steroids secreted from extrinsic to intrinsic layers designated as

- Zona glomerulosa which secretes mineralocorticoids as aldosterone ~Zona fasciculata which secretes glucocorticoids as cortisol
- Zona reticularis which secretes androgens as testosterone, dihydrotestosterone (DHT), androstenedione or dihydroepiandosterone (DHEA).
- Hyperaldosteronism or Conn's syndrome depicts elevated aldosterone levels which influences distal tubules and collecting ducts of nephron with increased sodium or water retention and decimated potassium retention with consequently elevated blood pressure along with hypernatremia and hypokalaemia.
- Cushing's syndrome exhibits enhanced levels of cortisol, decimated corticotrophin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) along with hyperglycaemia.
- Virilization denominates elevated dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEA-S), androstenedione, testosterone, dihydrotestosterone (DHT) and urinary 17-ketosteroids
- Feminization is associated with elevated androgens with aromatization along with enhanced oestrogen, oestradiol and urinary 17-ketosteroids [2,3].

Paediatric neoplasms arise in concurrence with predisposing genetic factors with ~50% children demonstrating adrenal cortical tumours as encountered with Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome. Aforesaid lesions may occur on account of defective apoptosis.

Neoplastic proliferation of adrenal cortical cells may emerge from diverse layers of adrenal cortex although lesions arising from zona fasciculata are commonly discerned [2,3].

Few adrenocortical adenomas are functional wherein the neoplasms which may engender a pure or mixed endocrine syndrome designated as

- Hhyperaldosteronism or Conn's syndrome comprised of hypertension, proximal muscle weakness, headache, polyuria, hypokalaemia, hypocalcaemia and tachycardia along with or devoid of palpitation ~hypercortisolism or Cushing's syndrome demonstrating central obesity, moon facies, plethora, striae, thinned out cutis, easy bruising, hirsutism, telangiectasia or hyperhidrosis
- Virilization manifests in
- Female subjects as enhanced muscle mass with Herculean habitus, clitoromegaly, facial hair, deep voice and pubic hair
- Male subjects as penile enlargement and pubic hair
- Feminization represents with gynecomastia or impotence [3,4].

Upon gross examination, adrenocortical adenoma appears as a unilateral, solitary, golden yellow tumefaction with dark areas concurrent with foci of haemorrhage, lipid depletion or elevated lipofuscin. Tumour magnitude is < 5 centimetres and tumour weight appears < 50 grams. Paediatric neoplasms may weigh up to 500 grams. Functional adenoma may terminate into atrophy of ipsilateral or contralateral adrenal cortex.

Upon cytological examination, distinction between adrenocortical adenoma and conventional adrenal cortex may be challenging. Of variable cellularity, loose clusters of enlarged cells pervaded with foamy or vacuolated cytoplasm and spherical to elliptical nuclei with smooth outline are encountered. Features such as naked nuclei, variable nuclear magnitude or contour appear insignificant [3,4].

Upon microscopy, neoplastic adenoma cells appear enlarged, imbued with abundant, foamy cytoplasm reminiscent of zona fasciculata or variable cytoplasm with significant nuclear pleomorphism or anisonucleosis and distinct cellular perimeter. Intrinsic balloon cells configuring Cushing's syndrome are composed of clusters of enlarged cells incorporated with lipid-rich cytoplasm.

Morphological variants composed of oncocytic cells or myxoid stroma may be encountered [3,4].

Upon ultrastructural examination, numerous intracytoplasmic lipid droplets of variable magnitude are observed. Cellular perimeter exhibits prominent micro-villous projections. Smooth endoplasmic reticulum is abundant. Spherical to elliptical mitochondria appear predominant. Cristae demonstrate tubular to vesicular configurations as encountered within zona fasciculata or lamellar profile as encountered within zona reticularis [3,4].

Figure 1: Adrenocortical adenoma delineating clusters of enlarged cells imbued with abundant, granular, eosinophilic or vacuolated cytoplasm and vesicular nuclei with significant anisonucleosis and a clear cellular perimeter [6].

Figure 2: Adrenocortical adenoma demonstrating nests of enlarged cells incorporated with abundant, granular, eosinophilic cytoplasm with vesicular nuclei and marked anisonucleosis [7].

TNM staging of adrenocortical carcinoma (AJCC 8th edition) [3,4].

Primary tumour

- TX: Tumour cannot be assessed
- T0: No evidence of primary tumour
- T1: Tumour magnitude ≤5 centimetres with absent invasion into per-adrenal tissues
- T2: Tumour magnitude >5 centimetres with absent invasion into peri-adrenal tissues
- T3: Tumour of variable magnitude with invasion into peri-adrenal adipose tissue
- T4: Tumour of variable magnitude with invasion into abutting organs as pancreas, spleen, hepatic parenchyma, renal parenchyma or large blood vessels as inferior vena cava or renal vein.

Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed
- N0: Regional lymph node metastasis absent
- N1: Regional lymph node metastasis present.

Distant metastasis

- M0: Distant metastasis absent.
- M1: Distant metastasis present into sites such as hepatic or pulmonary parenchyma.

Adrenocortical adenoma is immune reactive to **α-inhibin**, MelanA/Mart1, steroidogenic factor-1 (SF-1), calretinin, BCL2 or D2-40. Staining of fresh, frozen tumour cells with Oil Red O is optimal for highlighting intracytoplasmic lipid.

Adrenocortical adenoma is immune non reactive to epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), B72.3, S100 protein, chromogranin, vimentin, carbonic anhydrase IX (CAIX), synaptophysin, neuron specific enolase (NSE) and low molecular weight cytokeratin as AE1/AE3 or CAM 5.2. Ki67 proliferation index is < 5% [4,5].

Adrenocortical adenoma requires segregation from neoplasms such as adrenocortical carcinoma, cortico-medullary adenoma, hepatocellular carcinoma, malignant melanoma, metastatic carcinoma, pheochromocytoma or clear cell variant of renal cell carcinoma. Besides, lesions such as nodular hyperplasia, cysts, myelolipoma, angiomyolipoma, haemangioma, hamartoma or granulomatosis require exclusion.

Adrenocortical adenoma may be discovered incidentally during imaging procedures for unrelated lesions. Therein, cogent clinical symptoms or detectable hormonal anomalies remain absent or undetected.

Generally, simple observation, serial imaging, precise biochemical or haematological parameters, fine needle aspiration or core needle tissue samples may be adopted for appropriate neoplastic discernment and excluding metastasis from non-adrenal primaries [4,5].

Tumefaction configures a well circumscribed lesion comprised of cellular constituents of three layers of normal adrenal cortex.

Differentiation of adrenocortical adenoma from normal adrenal cortex within adrenal core needle tissue samples may be challenging.

Paediatric neoplasms may demonstrate atypical histologic features wherein segregation of adrenocortical adenoma from adrenocortical carcinoma may be challenging [4,5].

Employed endocrine tests appear within normal limits. Few neoplasms depict subclinical hormone production with minimal abnormalities. Generally, endocrine assays as dexamethasone suppression test, serum adrenocorticotrophic hormone (ACTH) levels, plasma free metanephrine/normetanephrine, 24 hour total urinary metanephrines and ratio of plasma aldosterone: plasma renin require evaluation [4,5]. Computerized tomography (CT) exhibits a spherical, homogenous, well delineated neoplasm demonstrating a distinctive zone and absence of tumour extension into adjacent anatomical structures.

Non contrast computerized tomography depicts decimated attenuation ≤10 Hounsfield units, in contrast to uninvolved adrenal parenchyma. Besides, neoplasm may be contrast enhancing.

Magnetic resonance imagining (MRI) is adopted to visualize microscopic foci of mature adipose tissue, a feature favouring adrenocortical adenoma. Also, 'chemical shift' phenomenon comprised of elevated 'in phase' signal intensity and decimated 'out of phase' signal is encountered.

18 fluoro-deoxy glucose positron emission tomography (18FDG-PET) exhibits enhanced uptake of 18FDG within malignant lesions, in contrast to uninvolved parenchyma [4,5].

Majority of adrenal lesions > 4 centimetre magnitude necessitate surgical extermination, irrespective of imaging features, on account of enhanced possible occurrence of adrenocortical carcinoma. Enlarged neoplasms > 4 centimetre diameter occur as functional lesions and mandate surgical resection.

Miniature lesions < 4 centimetre magnitude occur as non functional tumours which appear benign upon imaging and may be managed with clinical observation and follow up [4,5].

Annual assessment of biochemical parameters for initial four years is necessitated in order to evaluate functional status of the neoplasm. Repetitive computerized tomography at 6 months to 12 months following initial tumour diagnosis is employed. Static neoplasms with absent progression do not mandate additional monitoring.

Distinction of adrenocortical adenoma from adrenocortical carcinoma can be challenging. Generally, microscopic features as tumour magnitude, tumour necrosis, mitotic activity and atypical mitoses are reliable indicators of malignant metamorphosis [4,5].

Weiss diagnostic criterion as elevated mitotic rate, atypical mitoses, enhanced nuclear grade, minimal percentage of clear cells, necrosis, diffuse tumour architecture, capsular invasion, sinusoidal invasion or venous invasion can be employed to assess malignancy wherein a score of ≥3 is decisive.

Modified Weiss criterion as > 5 mitoses per 50 high power fields, < 25% constituent clear cells, atypical mitotic figures, necrosis and capsular invasion can be adopted to evaluate malignant transformation wherein a score of ≥3 is decisive [4,5].

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6. Image 1 Courtesy: Wikimedia commons.

7. Image 2 Courtesy: Libre pathology