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Desultory and Glib-Adrenocortical Carcinoma

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Adrenocortical carcinoma is an exceptionally discerned, malignant, endocrine, epithelial tumour emerging from adrenal cortical cells. The heterogeneous neoplasm may be engendered due to overexpression of IGF2 and is associated with significant mortality. Majority of neoplasms appear as sporadic lesions although may demonstrate diverse syndromic settings. Prognostic outcomes are contingent to age of incriminated subject, clinical representation, tumour stage, precise histological variant and molecular or genomic characteristics of the neoplasm.

Additionally designated as adrenal cortical carcinoma (ACC), conventional subtype of adrenocortical carcinoma, adrenal cortical adenocarcinoma or malignant adrenal cortical tumour, the neoplasm configures around ~6.8% of primary adrenal neoplasms. Median age of disease occurrence is ~55 years although no age of disease emergence is exempt. A bimodal distribution of disease is encountered with peak occurrence within first decade and fifth decade. Caucasians are commonly implicated. A female preponderance is observed with male to female proportion of 1:1.5 - 2.5. Adrenocortical carcinoma is predominantly sporadic although ~10% instances arise within syndromic settings (1,2).

Adrenocortical carcinoma frequently depicts significant mutations within driver genes as IGF2, CTNNB1, TP53, TERT, ZNRF3, PRKAR1A, RPL22, TERF2, CCNE1 or NF1. Neoplastic cells commonly demonstrate massive loss of DNA with subsequent duplication of whole genome, a feature which is accompanied by an aggressive clinical course and indicates disease progression. Elevated expression of TERT, decimated telomere length and activation of cell cycle programs are encountered.

Adrenocortical carcinoma preponderantly implicates left adrenal gland with left to right lesion proportion of ~1.2:1. Bilateral neoplasms are uncommonly encountered (~1%). Exceptionally, adrenocortical carcinoma emerges within ectopic adrenal rests confined within retroperitoneum, ovary, spinal canal or abdominal wall (1,2). Adrenocortical carcinoma may exhibit cogent molecular evidence of progression of an adrenal gland adenoma into overt carcinoma. Predominantly associated oncogene insulin-like growth factor 2 (IGF2) induces tumorigenesis. Besides, elevated mRNA and protein expression is encountered within adrenocortical carcinoma, in contrast to normal adrenal cortex or adrenocortical adenoma.

Majority (~90%) of neoplasms appear as sporadic lesions. Pertinent contributing factors as cigarette smoking with consequent occurrence of genomic mutation signatures and mismatch repair deficiency are discerned(1,2).

Sporadic neoplasms arise in concurrence with acquired genetic mutations of diverse driver genes as IGF2, CTNNB1, TP53, ATM, TERT, RB, ZNRF3 or PRKAR1A along with activation of cellular signalling pathways and significant accumulation of chromosomal alterations. Genetic susceptibility is encountered in up to 10% instances and cogent genetic screening is recommended (2,3).

Adrenocortical carcinoma concurs with diverse disorders as multiple endocrine neoplasia type 1 (MEN1), Lynch syndrome, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, adenomatous polyposis coli (APC), neurofibromatosis type 1 (NF1), Carney's complex and congenital adrenal hyperplasia. Paediatric neoplasms associated with Li-Fraumeni syndrome demonstrate accompanying germline mutation TP53 R337H (2,3).

Around ~50% of adrenocortical carcinomas are functional whereas ~50% tumours are non functional. Functional adrenocortical carcinoma delineates symptoms concurrent to hormone production as ~rapid onset and occurrence of Cushing's syndrome in ~50% neoplasms which depict excess of cortisol ~androgen secretion with hirsutism, virilization and menstrual disturbances in ~20% tumours delineating sex hormone secretion ~hypertension and hypokalaemia in ~8% tumefaction with aldosterone secretion ~up to 25% neoplasms enunciate mixed hormone secretion and concordant symptoms. Incriminated young, female subjects may represent with distant metastasis(2,3). Non functional adrenocortical carcinoma may manifest ~majority (80%) of neoplasms exhibit a mass effect with occurrence of gastrointestinal symptoms, organ compression or pain within lumbar region. Neoplasm may simulate an infectious process with emergence of localized pain and pyrexia due to cytokine secretion from neoplasms with significant necrosis. ~few (20%) neoplasms may emerge as an incidental discovery with imaging procedures adopted due to diverse non concordant conditions. Neoplasms may displace and infiltrate adjacent organs as pancreas, renal parenchyma, hepatic parenchyma, adrenal vein, inferior vena cava or retroperitoneum(2,3). Commonly, distant metastasis ensues into hepatic parenchyma (60%), regional lymph nodes (40%), pulmonary parenchyma (40%), peritoneal and pleural surface, retroperitoneum or bone. Diverse cutaneous surfaces exhibit metastasis from anaplastic tumours(2,3). Upon gross examination, a solitary, bulky, yellow, tan or reddish brown tumefaction is delineated. Generally, neoplasm weighs > 200 grams. Median tumour magnitude varies from 10 centimetres to 12 centimetres. Neoplasms of up to 28 centimetre diameter are documented. Cut surface is heterogeneous with focal necrosis and haemorrhage. Upon cytological examination, singular cells and inadequately cohesive cellular clusters appear disseminated within foci of tumour necrosis. Cellular cytoplasm is intensely eosinophilic or vacuolated. Nuclear atypia and mitotic activity is prominent(3,4).

Upon microscopy, the encapsulated tumefaction is comprised of cellular nests, enlarged sheets and trabeculae of variable magnitude circumscribed by dense fibrous capsule demonstrating foci of tumour cell infiltration. Besides, lymphatic invasion and vascular venous or sinusoidal tumour invasion may be discerned. Foci of tumour necrosis, haemorrhage or degeneration are frequently encountered. Enlarged cells are pervaded with granular, clear to eosinophilic cytoplasm. Pleomorphic cells are frequently encountered. Intra-nuclear inclusions, mitotic figures and atypical mitoses are commonly observed. Tumour grade is contingent to frequency of mitotic figures and is designated as ~low grade neoplasm depicting ≤ 20 mitoses/50 high power fields(hpf) ~high grade neoplasm delineating > 20 mitoses/50 high power fields(hpf)(3,4). Adrenocortical carcinoma represents with cogent morphological subtypes designated as ~conventional variant which denominates up to 90% instances ~oncocytic variant composed of > 75% oncocytic cells ~myxoid variant exhibiting abundant extracellular mucin ~sarcomatoid variant comprised of focal mesenchymal differentiation. Besides >one third (33%) of lesions demonstrate discontinuity of circumscribing reticular fibres or basement membrane network. Upon ultrastructural examination, abundant rough and smooth endoplasmic reticulum, intracytoplasmic lipid droplets, several mitochondria with tubular cristae and occasional dense core secretory granules are discerned. Secretory granules may be associated with immune reactive neuroendocrine markers (3,4).

Adrenocortical carcinoma can be appropriately staged with European Network of Study of Adrenal Tumours (ENSAT) which concurs with clinical outcomes and is designated as ~stage I: Tumour magnitude ≤ 5 centimetres ~stage II: Tumour magnitude > 5 centimetres wherein tumour is localized within stage I and stage II ~stage III: Tumour infiltration into surrounding soft tissue, regional lymph node metastasis or tumour thrombus incriminating inferior vena cava and/or renal vein ~stage IV: Tumour associated with distant metastasis(3,4)

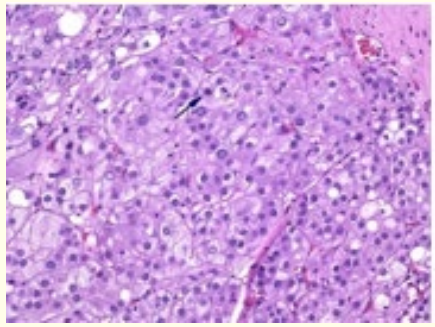

Figure 1: Adrenocortical carcinoma delineating nests and sheets of enlarged cells pervaded with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli and intra-nuclear cytoplasmic inclusions circumscribed and traversed by dense fibrous tissue. Foci of necrosis, haemorrhage and mitotic activity are encountered (6).

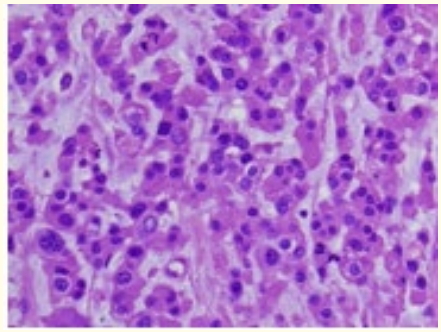

Figure 2: Adrenocortical carcinoma demonstrating aggregates and cellular clusters of enlarged cells permeated with abundant eosinophilic cytoplasm, vesicular nuclei and intra-cytoplasmic nuclear inclusions and traversing fibrous tissue stroma (7).

Parameter	***Score***
Nuclear grade III/IV(Fuhrman)	1
Mitotic figures>5 per 50 hpf	1
Atypical mitosis	1
Necrosis	1
Diffuse architecture>30% of tumour volume	1
Clear cells≤25% of tumour volume	1
Capsular invasion	1
Venous invasion	1
Sinusoidal (lymphatic) invasion	1
Total score	9

Score of ≥3 is diagnostic of adrenocortical carcinoma.

Table 1: Weiss scoring system of adrenocortical carcinoma (3,4).

Parameter	*Score*
Mitotic figures >5 per 50 hpf	2
Clear cells ≤25% of tumour volume	2
Atypical mitosis	1
Necrosis	1
Capsular invasion	1
Total score	7

Score of ≥3 is diagnostic of adrenocortical carcinoma.

Table 2: Modified Weiss system (3,4).

Adrenocortical carcinoma is immune reactive to steroidogenic factor 1 (SF1), calretinin, inhibin, MelanA / MART1, synaptophysin, neuron specific enolase (NSE), IGF2, vimentin, p53, INSM1 or CAM 5.2. Reticulin stain exhibits a significantly disrupted cellular framework. Adrenocortical carcinoma is immune non reactive to PAX8, CAIX, CD10,CK7, CK20, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), GATA3, S100 protein, arginase, HepPar1, glypican and chromogranin(4,5).

Adrenocortical carcinoma necessitates segregation from neoplasms such as adrenal cortical adenoma, pheochromocytoma, clear cell variant of renal cell carcinoma, hepatocellular carcinoma or distant metastasis from pulmonary neoplasms, malignant melanoma, carcinoma breast, colorectal carcinoma or carcinoma of urinary bladder. Besides, distinction is required from ACTH independent cortisol producing adenoma, adrenal hyperplasia, adrenocortical autoantibodies, polycystic ovarian disease, ovarian hyperthecosis or congenital adrenal hyperplasia (CAH). Localized tumour infiltration or distant metastasis emerge as definitive criteria of ascertaining malignant metamorphosis(4,5). Imaging can be optimally adopted to demarcate adrenocortical adenoma from adrenocortical carcinoma. However, categorization of benign tumours demonstrating significant haemorrhage or revascularization may be challenging.

Characteristically, adrenocortical carcinoma emerges as an enlarged tumour with irregular, infiltrative perimeter. Computerized tomography (CT) and magnetic resonance imaging (MRI) demonstrates signal heterogeneity of the neoplasm. Functional fluorodeoxyglucose positron emission tomography (PET) imaging is beneficial in discerning distant metastases and may ameliorate diagnostic outcomes. Absence of or disruption of reticulin framework contributes as a distinguishing feature between adrenocortical carcinoma and adrenocortical adenoma(4,5). Serum or urine hormone quantification of free cortisol, ACTH, DHEA sulphate, 17-OH, 17-hydroxy testosterone, 17-beta-oestradiol or 17-deoxycortisone is recommended. Dexamethasone suppression test, serum potassium levels and steroid metabolome profiling with mass spectrometry can be optimally adopted for tumour diagnosis. Computerized tomography (CT) and magnetic resonance imaging (MRI) of abdominal cavity demonstrates decimated lipid content, in contrast to adrenocortical adenoma. A heterogeneous, enlarged tumefaction > 5 centimetre magnitude with image enhancement is encountered. Upon computerized tomography, malignant neoplasms may exemplify a magnitude of 46 millimetres and radio-density of 20 Hounsfield units. Neoplasm depicts an irregular perimeter and focal necrosis or calcification. Infiltration or displacement of adjacent organs may ensue along with tumour extension into inferior vena cava. Positron emission tomography (PET) can be beneficially adopted to detect distant metastasis(4,5). DNA methylation signatures may be employed to identify cogent molecular subtypes of adrenocortical carcinoma delineating distinct clinical outcomes with proportionate disease progression of 7%, 56% and 96%.

Adrenocortical carcinoma may optimally be subjected to radical surgical resection. Localized tumours may be treated with dissection of regional lymph nodes. Surgical extermination of solitary metastases into pulmonary parenchyma is recommended. Besides, metachronous resection of metastasis may be advantageously adopted(4,5). Adjuvant radiation therapy is beneficial for ~neoplasms with ruptured capsule or tumour confined to surgical margins ~tumours unamenable to surgical resection or oligo-metastatic neoplasms, especially with bone metastasis. Therapy with mitotane, an adrenolytic drug which is a derivative of insecticide dichlorodiphenyltrichloroethane (DDT) is commonly employed as an adjuvant agent following incomplete surgical resection, in subjects ineligible for surgical intervention and in metastatic neoplasms. The agent is accompanied by severe toxicity and side effects wherein

various biomarkers as RRM1 or CYP2W1 may be employed to predict therapeutic response of mitotane(4,5). Additionally, agents such as ~systemic standard chemotherapy with etoposide, doxorubicin, cisplatin and mitotane (EDP-M) ~immunotherapy with checkpoint inhibitors as nivolumab or pembrolizumab ~targeted therapy with sunitinib, c MET inhibitors, cabozantinib, IGF1 inhibitors, m TOR inhibitors or VEGF inhibitors may be beneficially utilized. Adrenocortical carcinoma demonstrates an inferior prognostic outcome with 5 year mortality of 50% to 90%. Besides, magnitude of incriminated organ within a confined tumour necessitates evaluation(4,5). Tumour stage is a significant prognostic indicator wherein ~pT1 with tumour magnitude ≤ 5 centimetres depicts a 5 year survival of 82% ~pT2 with tumour magnitude > 5 centimetres delineates a 5 year survival of ~61%. Majority of neoplasms are associated with tumour invasion wherein ~pT3 neoplasms exhibit localized tumour invasion and 5 year survival of ~56% ~pT4 neoplasms exemplify metastasis into adjacent organs as diaphragm, pancreas, spleen, renal parenchyma, hepatic parenchyma and 5 year survival of ~37%(4,5). Distant metastases upon initial disease representation is encountered in ~40% instances with 5 year survival of 0% to 18%. Hormone producing tumours manifest ~hypercortisolism contributes as an adverse prognostic factor, especially in subjects with complete surgical eradication of disease. Age of incriminated subject represents as a prognostic indicator(4,5). Factors contributing to superior prognostic outcomes appear as ~children < 5 years upon initial tumour diagnosis ~complete surgical resection of tumour ~neoplasm < 400 grams ~ tumours demonstrating < 15 mitotic figures/20 high power fields ~minimal tumour necrosis. Neoplasm occurring in adults or individuals > 50 years is an independent prognostic factor with increased tumour associated mortality(4,5). Microscopic features contributing to prognostic outcomes represent as ~mitotic activity which appropriately defines low grade carcinoma with< 20 mitoses per 50 high power fields and high grade carcinomas with ≥ 20 mitoses per 50 high power fields ~proliferation rate assessed with Ki67 labelling index delineates significant prognostic and predictive outcomes, especially in grade 2 and grade 3 neoplasms ~angio-invasion is a superior microscopic indicator of adverse prognostic outcome ~oncocytic, myxoid and sarcomatoid variants exhibit variable prognostic outcomes(4,5) Prognostic biomarkers appear concurrent with inferior clinical outcomes and manifest as ~overexpression of IGF2, TOP2A, EZH2, MCM2, SOAT1, mTOR, BARD1, BUB1B or PINK1 genes ~loss of DAXX expression ~elevated SF1 expression ~elevated expression of miR-483-5p, miR-450a-5p, miR-210, miR421 ~minimal expression of miR-195 ~decimated expression of CXCR4 / CXCR7, PDL1 / PDL2 or CD276 ~transcriptome profiling is associated with varying proportionate survival within diverse groups ~three distinct molecular subtypes appear contingent to DNA methylation signatures with distinct clinical outcomes and proportionate disease progression at 7%, 56% and 96%(4,5).

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6. Image 1 Courtesy: Webpathology.com.
7. Image 2 Courtesy: Science direct.