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Solid Tumour Section

Mini Review

Endocrine/neuroendocrine glands: Adrenal cortical carcinoma

Constantine A Stratakis, Ludmila Matyakhina

Unit on Genetics & Endocrinology (UGEN), Developmental Endocrinology Branch (DEB), NICHD, NIH, Building 10, Room 10N262, 10 Center Drive, MSC 1862, Bethesda, MD 20892-1862, USA (CAS, LM)

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Identity

Alias

Adrenocortical Carcinoma; Adrenal Tumor

Note

Adrenocortical carcinoma is a rare malignant neoplasm of adrenal glands, which most often presents without any hormonal symptoms. The most common clinical presentation of patients with hormone-secreting adrenocortical carcinoma is that of Cushing's syndrome.

Other hormonal hypersecretion syndromes associated with adrenocortical carcinoma include virilization (from androgen-producing tumors), feminization (estrogen-producing tumors), and hyperaldosteronism.

Multiple hormones may be produced by a single tumor, causing a mixed clinical picture. In children, virilization is more common because carcinomas have a greater tendency to be presented with a hormonal syndrome.

Clinics and pathology

Etiology

Adrenal cancer may present as part of rare hereditary syndromes such as Wiedemann-Beckwith syndrome (WBS) linked to 11p15.5 or the Li-Fraumeni syndrome (LFS), associated with germline mutations of the TP53 gene, on 17p. Sometimes carcinomas develop in children with congenital adrenal hyperplasia (CAH) that is caused

most frequently by mutations in the CYP21B gene.

Epidemiology

Adrenal cancer is a rare malignancy representing only 0.05% and 0.2% of all cancers worldwide. Women tend to develop functional adrenal cortical carcinomas more commonly than men. Men develop non-functional malignant adrenal tumors more often than women.

There is a bimodal distribution in terms of age: young children less than 5 years old, and adults in their 30s and 40s. In Brazil, the incidence of carcinomas is three times more than the international rate.

Pathology

Grading and staging:

Stage I: disease confined to the adrenal gland without local invasion or distant metastases and the greatest tumor dimension less than 5cm.

Stage II: same as stage I but the greatest tumor dimension is greater than 5 cm.

Stage III: local invasion that does not involve adjacent organs or regional lymph nodes.

Stage IV: distant metastases or invasion into adjacent organs plus regional lymph nodes.

Treatment

Treatment for adrenocortical carcinomas is complete surgical resection; these tumors do not respond well to chemotherapy. Mitotane may be used as a chronic treatment in non-cured cases or prophylactically. Other medications (e.g. ketoconazole, metyrapone, aminoglutethimide) may be given to reduce production of cortisol and other adrenal steroids that is responsible for many of symptoms.

Prognosis

Extremely poor prognosis, with a survival rate at 20% at five years for stage I-II disease.Poor prognostic indicators include: age at diagnosis, tumor size, distant metastases, invasion of vessels, capsule, or adjacent organs, and tumor necrosis. Pediatric patients with a hormonal syndrome are considered to have a better prognosis because the associated signs and symptoms can make the cancer diagnosis easier leading to earlier surgical intervention

Cytogenetics

Morphological Cytogenetics

Only a few karyotyping studies has been performed. Chromosomal analysis revealed a modal number of 61 with consistent structural abnormalities of add(3)(q11), add(9)(p11), and add(16)(ql1) in one case of adult carcinoma and the karyotype 46, XX, t(4;11)(q35;p13) in the another one. Karyotyping of short-term cultured cells from an 11-cm adrenocortical carcinoma in a 3.5-year-old girl revealed the very complex karyotype 46,XX, inv(9)(p11q12)c/[2]/56-57,XX, +2, +4, +5, +7, +8, inv(9)c, +10, +add (13)(p11), +14, +15, +19, +20, +20, +mar[cp19].

Molecular Cytogenetics

Fluorescent in situ hybridization (FISH) studies of carcinomas showed increasing genome instability in carcinoma progression. Loss of heterozygosity (LOH) studies identified allelic losses on chromosomes 11p, 11q, 13q, and 17p. The LOH on 2p16 is strongly associated with the malignant phenotype.

Several studies were reported in carcinomas with comparative genomic hybridization (CGH). DNA sequence copy number gains were identified on chromosomes 4, 5, 9q, and 12q and losses on chromosomes 17p, 1p, 2q, 11q, and 9p. All studies showed that the number of genomic changes is closely correlated with tumor behavior. In adenomas, small tumors contain a small or zero number of chromosomal imbalances, and a number of changes increases in larger adenomas and then considerably increases in carcinomas. Of adenomas, the most common alterations were gains of 4q, 17p, 17q and 9q32-qter. Two CGH studies of childhood adrenal tumors showed extensive genetic alterations both in benign and malignant tumors. The copy number changes are distinctly different to those seen in adult tumors thus possibly reflecting different genetic background for these tumors. High-level amplification of 9q34 was very common.

Genes involved and proteins

Note

A number of genes are implicated in tumor progression from adrenal adenoma to carcinoma; they include both oncogenes and tumor suppressor genes. Progression from adenoma to carcinoma involves a monoclonal proliferation of cells, which, together with other defects, have undergone rearrangements of the chromosomal locus 11p15.5 associated with IGF II hyperexpression and abrogation of expression of the CDKN1C and H19 genes. TP53 is involved in progression to carcinoma in a subset of patients. In childhood ADCC, 50% of children carried germline mutations of TP53. Deletions of the ACTH receptor gene have been recently found in undifferentiated adenomas and in aggressive adrenocortical carcinomas although the frequency of ACTH receptor deletion needs to be more fully examined. Other key oncogenes and tumor suppressor genes remain to be identified although the chromosomal loci that harbor them were identified at 17p, 1p, 2p16, 11q13, and 9p for tumor suppressor genes and chromosomes 4, 5, 9q, and 12 for oncogenes. The 11q13 region harbors the MEN1 gene, however mutations of the gene were not found in adrenal tumors.

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