Adrenocortical Carcinoma
A Clinician's Perspective

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KEYWORDS

• Adrenocortical carcinoma • Adrenal cortex tumors • Rare malignancies • Mitotane
• Platinum-based chemotherapy

Key points

- Adrenocortical carcinoma (ACC) diagnosis management often requires a multidisciplinary approach.
- Most cases are sporadic, although specific cancer syndromes have been identified with increased incidence of ACC.
- Approximately 60% of ACC tumors are functional and present with signs and symptoms related to production of excess hormones.
- Careful consideration should be given to the clinical context and manifestations of an adrenal tumor before obtaining pathology specimens.
- Although multidisciplinary approaches to ACC may result in long-term disease control and survival, conventional chemotherapy is not curative and newer targeted therapies have not yielded any significant impact on disease trajectory.

ABSTRACT

Within the category of orphan diseases and rare malignancies, adrenocortical carcinoma (ACC) represents an aggressive entity with high mortality and morbidity. While localized tumors which are diagnosed early can be cured with surgical intervention, there are prognostic factors which predict for micrometastases and consequent recurrent and advanced disease. In such cases, mitotane and cytotoxic chemotherapy have been utilized with a modest degree of benefit. The poor prognosis of recurrent and advanced ACC has underscored the interest in nuanced characterization of ACC cases to guide the personalized use of immunotherapeutic and novel targeted therapies.

OVERVIEW

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy of the adrenal cortex with an annual US incidence of approximately 1 to 2 new cases per million population.[1,2] Overall, ACC carries a poor prognosis, with the most consistent prognostic factor being the tumor stage at the time of diagnosis.[3] Unfortunately, retrospective studies have reported a 5-year survival rate of 24% for stage III and 0% for stage IV disease.[4]

ACC diagnosis (see also Pinto and Barletta, Adrenal Tumors, Surgical Pathology Clinics, 2015, Volume 8, Issue 4) and management often requires a multidisciplinary approach, frequently involving a medical oncologist, an endocrine surgeon, an endocrinologist, a pathologist (preferably one with endocrine expertise), and other disciplines. Approximately 80% of patients with localized disease will recur after complete resection.[5–7] With regard to recurrent or advanced disease, ACC is modestly responsive to standard cytotoxic chemotherapies, although various combinations have shown palliative benefit. Radiation and ablative techniques have been used with variable benefit depending on the clinical scenario.

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PATHOGENESIS

Most cases are sporadic, although specific cancer syndromes have been identified with increased incidence of ACC (**Table 1**). Sporadic cases have been proposed to develop through a sequence of genetic defects that are progressively acquired, ultimately resulting in malignant transformation.[8–11] TP53 is a frequently mutated gene in ACC and has been implicated in approximately one-third of sporadic ACC cases; loss of heterozygosity (LOH) at the 17p13 locus has been a frequent associated finding. Similarly, overexpression of insulinlike growth factor (IGF)-II, whose gene is located on chromosome 11, has been associated with sporadic ACC cases resulting from LOH at the 11p15 locus.[12,13]

Constitutive activation of beta-catenin in the Wnt signaling pathway as a result of activating somatic mutation of the *CTNNB1* gene has been identified as a frequent alteration in malignant adrenocortical tumors.[14] Wnt/beta-catenin pathway activation has been shown to be an independent predictor of less favorable disease-free and overall survival in patients with resected primary adrenal carcinoma.[15] Using present day exome sequencing techniques and nucleotide polymorphism arrays, a spectrum of mutations can be revealed in any given sporadic case. Although each such finding is not clinically actionable, we do appreciate that such genetic features can help differentiate patients with ACC with poor or good outcomes.

CLINICAL

Approximately 60% of ACC tumors are functional and present with signs and symptoms related to production of excess hormones. Cushing syndrome is a notable cause of morbidity and is the most frequent presentation in 45% of cases as compared with a mixed Cushing and virilization syndrome characterized by both glucocorticoid and androgen excess in 25%.[16,17] Glucocorticoid excess causes weight gain, fatigue, muscle weakness, and insomnia progressing over the course of months. Feminization and hyperaldosteronism occur in fewer than 10% of cases.[16] Virilization alone manifests in fewer than 10% of cases, but in the context of an adrenal lesions, this finding tends to be most suggestive of ACC.

In contrast, nonfunctioning ACCs include those with normal or subclinical production of hormones. These tumors are usually discovered incidentally when imaging is obtained for other reasons or as a consequence of a local mass effect or metastatic disease progression.

DIFFERENTIAL CONSIDERATIONS

Careful consideration should be given to the clinical context and manifestations of an adrenal tumor before obtaining pathology specimens. Suspicion of pheochromocytoma, for example, must be approached by biochemical testing as opposed to biopsy. Findings of hyperaldosteronism, hyperandrogenism, or Cushing syndrome provide added insight into the differential of an adrenal tumor. In attempting to rule out an ACC, cytology from a specimen obtained by fine-needle aspiration (FNA) is typically not adequate to distinguish between a benign mass and ACC (see also Pinto and Barletta, Adrenal Tumors, Surgical Pathology Clinics, 2015, Volume 8, Issue 4). Instead, FNA of an adrenal mass is more useful to characterize a metastatic lesion if there is sufficient suspicion that a different primary malignancy has metastasized to the adrenal gland.[18]

Several markers, such as alpha-inhibin, Melan A, and SF-1, can confirm the primary adrenal origin of a tumor (see also Pinto and Barletta, Adrenal Tumors, Surgical Pathology Clinics, 2015, Volume 8, Issue 4), but to distinguish ACC from a benign

Table 1
Cancer syndromes associated with increased incidence of ACC

Syndrome	Characteristics
Li-Fraumeni syndrome	Inactivating mutations of the *TP53* tumor suppressor gene on chromosome 17p with risk of breast cancer, soft tissue and bone sarcoma, brain tumors, and ACC.
Beckwith-Wiedemann syndrome	Abnormalities in 11p15 with risk of Wilms tumor, neuroblastoma, hepatoblastoma, and ACC.
Multiple endocrine neoplasia type 1 (MEN1)	Inactivating mutations of the *MEN1* gene on chromosome 11q. With risk of parathyroid, pituitary, and pancreatic neuroendocrine tumors, adrenal adenomas, and carcinomas.

Abbreviation: ACC, adrenocortical carcinoma.