Adrenocortical Carcinoma with Hypercortisolism

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KEYWORDS

• Adrenocortical carcinoma • Cortisol • Cushing syndrome • Mitotane

KEY POINTS

- Adrenocortical carcinoma (ACC) is a rare cause of Cushing syndrome.
- Prompt diagnosis and treatment are important because of its aggressive behavior. Clinical presentation of Cushing syndrome may be atypical because of cancer-related signs.
- The biochemical hallmarks of Cushing syndrome caused by ACC are adrenocorticotropic hormone (ACTH)-independent hypercortisolism and frequent concomitant hypersecretion of other steroids (precursors and/or androgens).
- The radiological phenotype of ACC on the computed tomography (CT) scan features its large size, high-density, intratumoral necrosis.
- Surgery is the treatment of choice and should be attempted whenever a radical resection is feasible.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive tumor with an annual incidence between 0.7 and 2 cases per million population. ACC is more frequently detected in women (55%–60%) and certain age groups (fourth and fifth decades); however, ACC can occur at any age.[1] ACC can affect children, with an exceedingly high incidence reported in southern Brazil because of the high prevalence of a TP53 germline mutation.[2] ACCs most frequently present as sporadic tumors, but can be encountered in the setting of hereditary tumor syndromes, such as Li Fraumeni (TP53 germline and somatic mutations), familial adenomatous polyposis coli (β-catenin somatic mutations), and Beckwith–Wiedeman (IGF-2 overexpression).[3]

Patients with ACC have an extremely poor prognosis, with an overall 5-year survival rate between 16% and 47%.[4] Prognosis is mainly influenced by completeness of surgical removal and tumor stage at diagnosis, with a 5-year stage-dependent survival of

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Endocrinol Metab Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.ecl.2018.02.003 **endo.theclinics.com**

81%, 61%, 50%, and 13%, respectively, from stage 1 to stage 4.[5] However, ACC is a heterogeneous disease with variable survival at any stage depending on molecular, pathologic, and clinical factors that have only been partially ellucidated.[6] One of the factors influencing the clinical phenotype of ACC patients is the functional activity of the tumor, which may result in different endocrine syndromes.[3,4,6] Manifestations of adrenal steroid hormone excess represent the most common presentation of ACC in up to 60% of cases[4] (**Fig. 1**). Patients with nonfunctioning ACC present with back or abdominal pain, nausea, vomiting, or less frequently fever and weigh loss. Also, in an increasing number of patients, ACC is discovered serendipitously, due to the widespread application of high-resolution cross-sectional scans.[7]

CLINICAL PRESENTATION

ACC has the propensity to produce and secrete steroids; thus, in all patients with a suspected ACC, signs and symptoms of cortisol, aldosterone, and sex steroids should be actively investigated[4] (**Box 1**). Concomitant secretion of different steroids is a hallmark of ACC. Pure estrogen excess is rare and may cause gynecomastia, loss of libido, and testicular atrophy in men.[8]

Patients with cortisol-secreting ACC exhibit facial plethora, easy bruising, weight gain, proximal myopathy, severe hypertension, and uncontrolled diabetes mellitus. Hypokalemia is common with severe hypercortisolism, because mineralocorticoid receptors are triggered by the large amount of cortisol that overwhelms the inactivating capacity of corticosteroid 11β-dehydrogenase isoenzyme 2 (HSD11B2). Women frequently complain of acne, hirsutism, and oligomenorrhea.[4] The differential diagnosis in these situations is polycystic ovary syndrome (PCOS), especially with mild or subclinical hypercortisolism. Clinical clues that are helpful to the diagnosis of ACC are the concomitant existence of Cushingoid phenotype with signs of marked androgen excess, or Cushing phenotype along with cancer-related symptoms (eg, anorexia, cachexia, or mass effect). With rapidly growing tumors, cancer-related features dominate the clinical presentation. ACC can also cause deep venous thrombosis or pulmonary embolism because of either cortisol excess or malignancy.[4] Cortisol

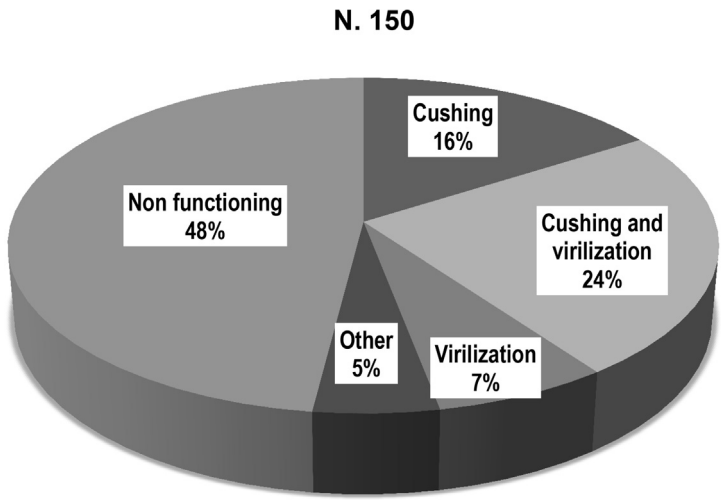

Fig. 1. Hormonal secretion in patients with ACC (S. Luigi series).