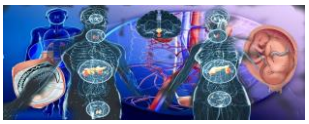
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An Epigenetic Aspects of Adrenocortical Carcinoma Diagnosis and Management

Hadjadj G, Gao T*, Le Tourneau T, Valente EU, Ragazzon R

Department of Health Sciences, Debre Markos University, Ethiopia

***Corresponding Author**: Gao T, Department of Health Sciences, Debre Markos University, Ethiopia.

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Abstract

Adrenocortical carcinoma (ACC) is a rare, aggressive malignancy with an annual incidence of ~1 case per million population. Differentiating between ACC and benign adrenocortical tumors can be challenging in patients who present with an incidentally discovered adrenal mass, due to the limited specificity of standard diagnostic imaging. Recently, urine steroid metabolite profiling has been prospectively validated as a novel diagnostic tool for the detection of malignancy with improved accuracy over current modalities. Surgery represents the only curative treatment for ACC, although local recurrence and metastases are common, even after a margin-negative resection is performed. Unlike other intra-abdominal cancers, the role of minimally invasive surgery and lymphadenectomy in ACC is controversial.

Keywords: Molecular profiling studies; adrenocortical carcinoma; endocrine malignancy; curative surgical resection; ACC tumorigenesis

Introduction

In recent years, it has become evident that patients with malignant disease are best cared for by multidisciplinary teams of physicians and associated healthcare providers. This is particularly true for rare disorders such as adrenocortical carcinoma (ACC). The care for patients with rare diseases by the nonexpert is often based on extrapolation from other more common diseases or from the scarce evidence available through the medical literature. The formation of dedicated multidisciplinary clinics providing care for a larger referral community (eg, state- or nationwide) is a crucial step in gathering, preserving, and enhancing knowledge about these uncommon disorders.

A multidisciplinary team that can provide high-level care for ACC patients ideally consists of endocrinologists, endocrine surgeons, medical and radiation oncologists, pathologists, radiologists, nuclear medicine physicians, and genetic counselors as well as clinical research coordinators. At the University of Michigan Health Systems, a multidisciplinary endocrine oncology program, mainly caring for patients with ACC has been in place for over 10 years.

Epidemiology

Adrenal tumors are very common, affecting 3% to 10% of the human population, and the majority are small benign nonfunctional adrenocortical adenomas (ACA). ACC, in contrast, is a very rare disease. The National Institutes of Health Office of Rare Diseases Research defines rare diseases by a prevalence of fewer than 200 000 affected patients in the United States. According to this definition, ACC might be regarded as an ultrarare disease. The median age of diagnosis is in the fifth to sixth decade, with the German ACC Registry reporting a median age at diagnosis of 46 years. This is in accordance with a median age of 46 years in a large single center series in France. Analysis of the SEER database gives a slightly older mean age of 55 years. Whether a second peak of increased incidence during childhood can be detected seems to be dependent on the prevalence of regional predisposing factors and biases. Epidemiological data on ACC from larger cancer registries is sparse, and they are often grouped with other endocrine malignancies, which makes analysis challenging. In addition, detailed analyses of ACC patients' family histories have not been systematically conducted. However, there are certain clinical features supporting genetic predisposition. ACC appears to be relatively more

Multiple endocrine neoplasia type 1 (MEN1) is caused by mutations in the *MENIN* gene on chromosome 11q13. Its classical manifestations are hyperparathyroidism, caused by 4-gland hyperplasia, foregut neuroendocrine tumors (most commonly in the pancreas and duodenum, but also thymus and lung), and pituitary adenomas (prolactinomas are most common). Associated adrenal lesions, mainly ACAs and uni- or bilateral hyperplasia, occur in 20% to 55% of MEN1 cases. Although hormone production has been well-described for adrenal tumors in MEN1, most of the tumors are nonfunctional. A small fraction of patients with MEN1 will develop ACC. Recent analysis of a French multicenter registry determined that ~10% of MEN1 patients have distinct adrenal tumors, and of these, up to 14% are malignant.

Pathology

The pathological assessment is the key to the final diagnosis of ACC, but it remains challenging. First, as the ACC can be non-secreting tumor, the adrenocortical origin of the mass must be established. The determination of steroidogenic factor 1 (SF-1) expression has proved as the most valid marker, Second, multiple parameters (macroscopic and microscopic) have to be evaluated in order to discriminate benign from malignant tumor.

Macroscopy revelead that ACC are usually large, heterogeneous, with a surface range from brown to orange to yellow depending on the lipid content of their cells. Necrosis is almost always present. Importantly, the presence of a tumoral invasion at different levels, as the tumor capsule, the extra-adrenal soft tissue or direct invasion of lymphatic channels, blood vessels are the key features of ACC.

Staging

Tumor staging is a widely used tool to assess prognosis in patients with cancer. For ACC, the tumor–node–metastasis (TNM) classification proposed by ENS@T is recommend. This staging system, defines stage I and stage II as strictly localized tumors with a size of ≤5 or >5 cm, respectively. Stage III ACC are characterized by infiltration in surrounding tissue, positive regional lymph nodes or a tumor thrombus in the vena cava and/or renal vein, whereas stage IV is defined by the presence of distant metastasis.

Methylome, Transcriptome, MicroRNA, and ACC Clustering

The ENSAT study incorporated the recursively partitioned mixture model to show four different DNA methylation-based tumor clusters. Compared to benign adrenal cortical tumors, ACCs are globally more hypermethylated at the CpG islands in the promoter regions. Radiation therapy techniques
With regard to the adjuvant radiotherapy technique at our institution, we use radiotherapy for patients who have undergone an R1 or R2 resection. Patients who have had a complete (R0) resection are considered for adjuvant radiotherapy, although this decision is personalized on a case-by-case basis, accounting for individual disease and patient characteristics.

Conclusion

Other future areas of study in the adjuvant setting include whether dose escalation might deliver better rates of local control while still sparing the associated organs at risk by using highly conformal techniques. In cases of small tumors, this might be accomplished with ablative dosages delivered via a stereotactic body radiotherapy technique. Finally, and most importantly, a prospective, multicenter trial is necessary to definitively establish whether adjuvant radiotherapy is effective in reducing local recurrences.

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