Adrenocortical Carcinoma: Update of Clinical Features and Diagnosis

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Abstract: Adrenocortical carcinomas represent about 0.02% of all malignant tumors. They can be either non-functional being incidentally diagnosed but large functional or non-functional tumors weighing above four kilos were also described. In this review we intended to correlate our experience in field of adrenocortical carcinoma with the literature data and to present our vision about their histogenetic aspects, the prognostic factors and molecular examinations in the field. The histological characteristics in routine Hematoxylin and Eosin stain were analyzed in relationship to the immunohistochemical antibodies such as Inhibin, Melan-A, HMB45, Keratin, Ki67, Synaptophysin, Chromogranin, Calretinin, Neuron specific enolase (NSE), RET, CD56, Vimentin, Epithelial Membrane Antigen (EMA). The histological subtypes such as myoxoid carcinoma and also the possible associated-lipomatous metaplasia, together with the differential diagnosis and the metastatic behavior, based on the newest data published in literature, were also discussed. The main purpose of the review was to present the clinico-pathological complexity of this rare but challenging and aggressive tumor.

Keywords: Adrenocortical carcinoma, diagnosis, EGFR, K-ras, lipomatous metaplasia, metastasis, myxoid adrenocortical carcinoma.

INTRODUCTION

Adrenocortical carcinomas (ACCs) are aggressive tumors that are very rarely diagnosed in the clinical practice. They account about 0.02% of all malignant tumors [1], with an annual incidence of 1 to 2 cases per million inhabitants [2]. In this review we intended to present the particularities of these tumors and also the clinico-pathological criteria used for their diagnosis, the differential diagnosis and the therapeutically possibilities.

CLINICAL ASPECTS

The ACCs are diagnosed in both children and adults, from 3 months to 91 years, with a slightly female predominance, the median age being about 56 years [2, 3].

They can be either functional or non-functional tumors. Depends on the secreted hormones, the functional tumors can associate high serum levels of cortisol, androgens and/or mineralocorticoids and also secondary Cushing's or Conn syndrome, along with uncontrolled hypertension [3, 4]. Gynecomastia in males/amenorrhea, hyperestrogenism or androgenism in females/virilisation in children can also be present [1, 3, 5]. Other nonspecific associated symptoms can also be seen, such as slight anemia or obesity.

The huge tumors can be sometimes palpated in the hypocondrium but the smallest ones are only diagnosed based on the inhomogeneous hypoechogenic mass located at the upper pole of the kidney at abdominal ultrasound examination. To confirm diagnosis, a computed tomography is necessary. Nonspecific radiologic findings were also reported [6].

METASTATIC BEHAVIOR

Several cases are diagnosed in late stages, sometimes the distant hematogenous-borne metastases being the first clinical signs. In most of the cases they are unilateral tumors but metastases in the opposite adrenal gland were also seen. Hepatic and pulmonary metastases were most frequently observed but, being very well-irrigated, they can spread throughout the body; ovary, skin, tongue, small intestine, colon, endobronchial mucosa and other organs were described as rare metastatic localizations [4, 7]. In one of our case we also identify a gastric metastasis in the submucosal layer of the stomach (case presentation is in press). The lymphatic spread is usually absent; mediastinal and neck lymph node metastases can be rarely seen [4, 7]. On the other hand, systemic metastases are identified between 17 to 53% of cases at the time of diagnosis [4]. The metastases occur in a period ranging from 0-100 months from the time of initial diagnosis. Tumor invasion is frequently seen in the renal or inferior vena cava [4].

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E-ISSN: 2309-6160/13

GROSS FEATURES

The ACCs are usually encapsulated tumors. They can be even small or huge tumors, weighing between 70 g and 4.7 kg [1, 5]. Although the tumor size is not a criterion to differentiate the malignant tumors from the benign ones, the adenomas are rather small and ACCs are rather huge.

The tumor is usually encapsulated and the external surface has a nodular or bosselated aspect. On the cut section, the nodular aspect is also observed, the solid area being admixed with gray gelatinous zones accompanied by hemorrhagic and necrotic areas. In about 3% of cases the tumor can have a cystic aspect [6].

MICROSCOPICAL FEATURES OF THE CLASSICAL TYPE

Although the immunohistochemical panel can help distinguishing ACCs from other endocrine tumors such as pheochromocytoma and also from a metastatic tumor, there is not a well-established consensus about the specifically markers. Based on this observation, the microscopical aspect observed in the usual staining Hematoxylin and Eosin, associated with the histochemical PAS-alcian blue staining, remains very important in these cases, the immunohistochemistry being only used to confirm diagnosis.

Most of ACCs are well-vascularized tumors, surrounded by a connective capsule that can or cannot

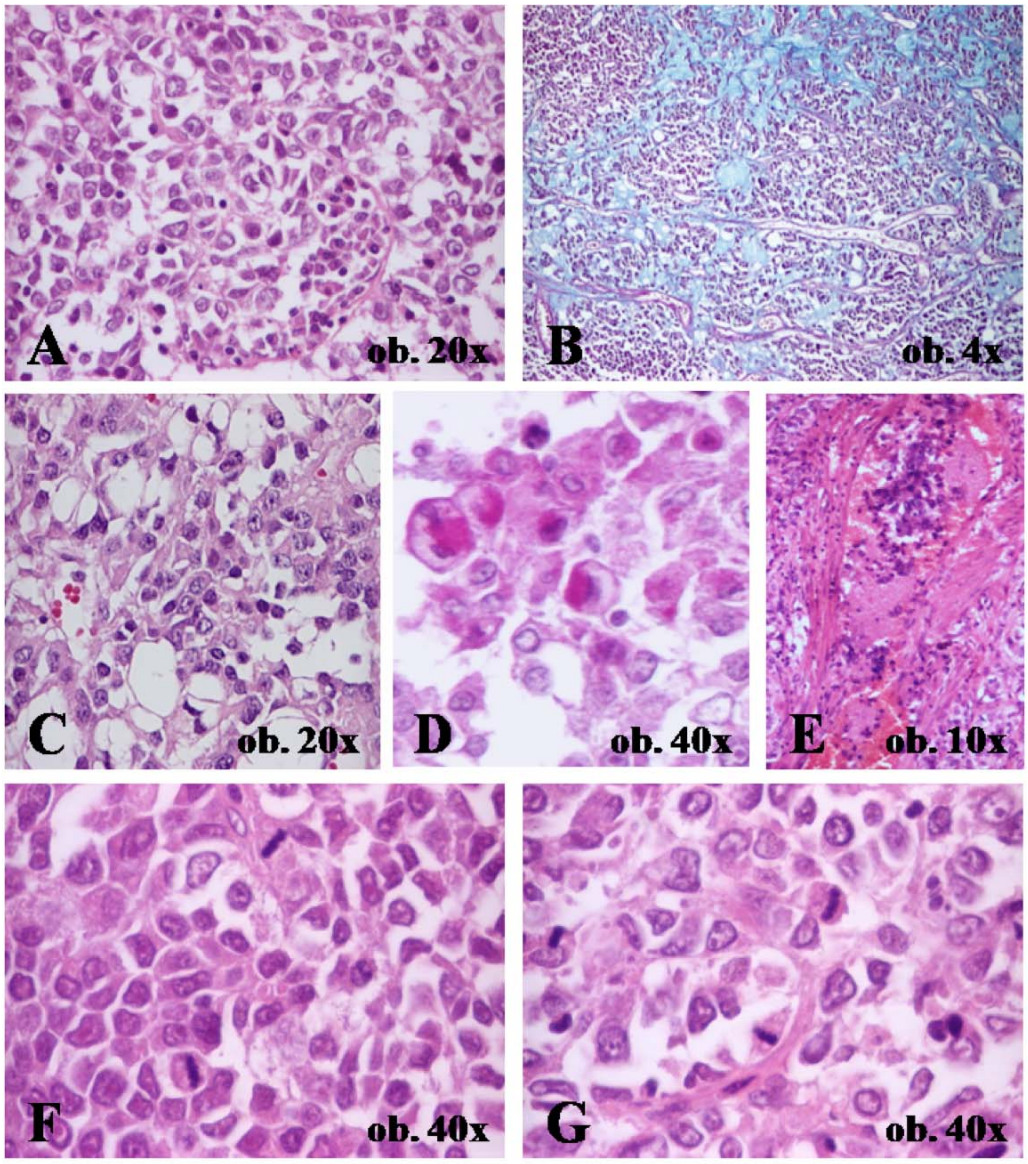

Figure 1: Microscopic features of adrenocortical carcinoma. **A**. Diffuse pattern of classical type; **B**. Myxoid subtype with alcian-blue-stained stroma; **C**. Lipomatous metaplasia; **D**. Pas-positive intracytoplasmic hyaline bodies; **E**. Tumor embolus with associated-platelets aggregation; **F**, **G**. Nuclear pleomorphism with a high mitotic rate (personal photos).

present tumor invasion. The tumor cells predominantly display a diffuse lobular architecture (>2/3 of tumor), the tumor sheets being separated by fibrous septa; trabecular or alveolar zones can also be seen. Large hemorrhagic and necrotic areas are also present. The high power view examination reveals large polygonal- or oval-shaped tumor cells with well-defined limits but cellular polymorphism can also be observed. Some of the tumoral cells can palisade around the blood vessels, similar to melanomas; a peritheliomatous arrangement was also described [8]. Capsular, sinusoidal and vascular invasion is necessary to be identified, as important prognostic factors. A variable amount of inflammatory cells and cellular debris can accompany the tumor cells proliferation [4].

Quite characteristic for this tumor is the cytoplasmic aspect that should be examined at high power fields (HPF). The cytoplasm can be slightly basophilic, eosinophilic or vacuolated, due to storage of lipids However, the vacuolization involves about 1/4 of the tumor area, compared to the adrenocortical adenomas in which the vacuolar cells are predominated; in normal glands and adenomas the lipids are intracytoplasmic stored but a lipid-depletion occurs during malignant transformation. Intracytoplasmic PAS-positive hyaline bodies are also characteristic but they do not occur in all of the cases (Figure **1**).

High nuclear pleomorphism, with large or even giant bizarre nuclei, and also a high mitotic rate (>20/50 HPF) with several atypical mitoses and well-defined nucleoli are specifically features [4].

Sometimes, lipomatous metaplasia or other particular aspects can be associated, their presence leading to a sub-classification of the ACCs. Some characteristics of these subtypes are present below in the paper. In one of our cases, osseous metaplasia was identified, this being probably related to the tumor-associated inflammation and necrosis.

Microscopical Subtypes

Beside of the above presented classical type-ACC, several variants have been described, such as follows:

- *Myxoid carcinoma* - a very rare variant, 27 cases being published to date [5, 9-12]; first case was diagnosed by Tang *et al.* in 1979, based on the light and electronic-microscope [10]. In these cases, the tumor stroma has a characteristic myxoid aspect, being Alcian blue positive and negative for PAS stain. This aspect can involve from 5% to 100% of tumor stroma, in the myxoid areas floated clusters of tumor cells being present in an acellular myxoid background (Figure **1**). The reticulinic network is partially preserved, being totally disintegrated in the myxoid areas [5, 9-12]

- *Myxoid carcinoma with lipomatous metaplasia* - in only one of the 27 reported myxoid carcinomas, associated lipomatous metaplasia was also mentioned [9] although we founded it in other two cases; the case presentation being in press (Gurzu *et al.* EGFR and K-ras wild-type giant myxoid adrenocortical carcinoma with lipomatous metaplasia and RET positivity. Personal communication - in press); however, this metaplasia is rather an intracellular lipid accumulation (Figure **1**); the cytoplasm of the involved tumor cells is stained by Sudan III and the nuclei are pushed to the periphery of the cells

- *Oncocytic carcinoma* - the tumor cells present an oncocytic feature and seems to have a more favorable prognosis but few of the published data regards their outcome [13]

- *Adrenocortical carcinoma with sarcomatous areas (sarcomatoid carcinoma, carcinosarcoma)* - six cases have been published to date; osteo-, chondro-, and rhabdomyosarcoma components but also malignant spindle cell component were described [14,15]. Rhabdoid adrenocortical carcinoma, for example, is necessary to be differentiated from metastatic rhabdoid tumors. It is usually diagnosed in adult females in their 5th decade of life, being rather non-functional. The tumor cells posses several intracytoplasmic eosinophilic inclusions, the nuclei are usually vesicular, with a signet-ring-like aspect and prominent nucleoli, with the same immunohistochemical features such as the classical ACC [14]

- *Adrenocortical carcinoma with adenosquamous differentiation* [16]

- *Pigmented carcinoma* - is a 'black adenoma' or 'pigmented adenoma' that display atypical histological features and can recur [17]

IMMUNOHISTOCHEMICAL PARTICULARITIES

As we already mentioned, the immunohistochemical panel is not pathognomonic and is rather use to

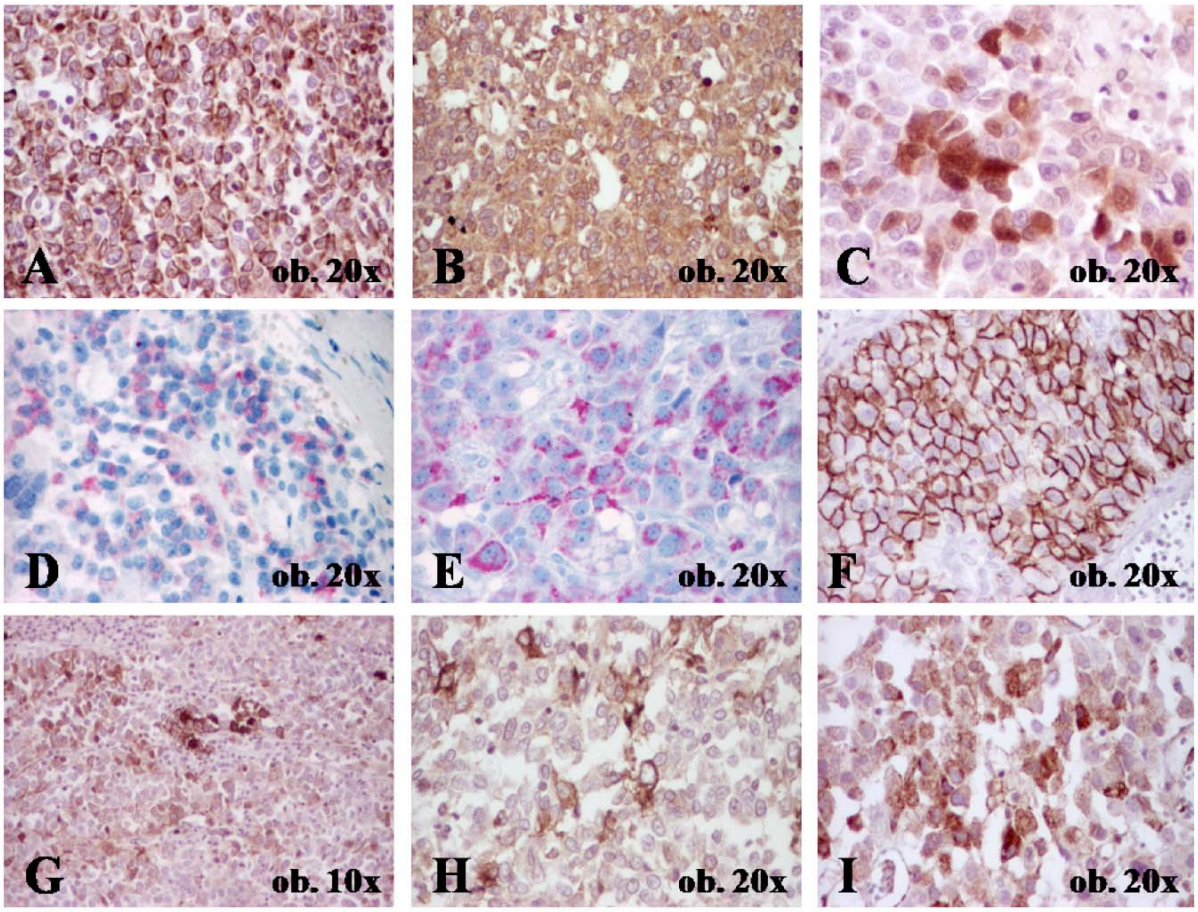

Figure 2: Immunohistochemical positivity of adrenocortical carcinoma for vimentin (**A**), synaptophysin (**B**), calretinin (**C**), inhibin (**D**), melan-A (**E**), CD56 (**F**), kerain AE1/AE3 (**G**), EMA (**H**), and RET oncoprotein (**I**) (personal photos).

confirm the diagnosis established based on the routine stains, the negative immunohistochemical reactions being also useful (Figure **2**). Despite the high mitotic rate and nuclear pleomorphism, the Ki67 proliferative index is about 5-30% [18] but the p53 nuclear positivity is usually higher than 40%. In most of the reported cases, the tumor cells displayed the following immunohistochemical features [7, 8, 14, 18, 19]:

- *Diffuse positivity* - Vimentin, Synaptophysin, Inhibin-α, Melan A, Calretinin
- *Focal positivity* - steroid receptor cofactor-1, Neuron Specific Enolase (NSE), CD56, c-KIT, Keratin AE1/AE3, Epithelial membrane antigen (EMA), RET oncoprotein, Vascular endothelial growth factor (VEGF), MART-1, Insulin-like growth factor II (IGF-II), Pax8
- *Negative stains* - Chromogranin, S100 (sustentacular cells can be positive), high molecular weight keratins (keratin 5,10,14), Keratin 7, Keratin 20, CEA (Carcinoembryonar antigen), HMB45, HER-2, CD10, CD31, CD34, CD68, Smooth muscle actin (SMA), bcl-2, cyclin D1.

MOLECULAR BIOLOGY

Little information about molecular examinations has been reported. In some of our cases we examined the mutations of K-ras (codon 12 and 13) and epidermal growth factor receptor (EGFR) genes (exons 18 through 21), no one presenting mutations; the results are in press. A Chinese team also denied EGFR mutations in ACCs [11]. Absence of K-ras mutations was recently confirmed by Hermsen *et al.* [20].

The mammalian target of rapamycin (mTOR) signaling pathway was proved to be implicated in the pathogenesis of ACC [21, 22]. 17p13/11p15 loss of heterozygosity (LOH) was reported to be present in some of the cases but it does not influence the survival rate [4].

Other molecular pathways, except the EGFR/K-ras and mTOR ones, should be explored to elucidate the genesis of ACC.

DIFFERENTIAL DIAGNOSIS

To establish a correct diagnosis, the ACC should be first differentiated from its benign and borderline counterparts, based on the light microscope, correlated with the clinico-pathological features, according to the Weiss's scoring index; presence of at least three criteria means malignancy, two of them indicating a borderline neoplasm [4, 5, 8, 12, 23]. We tried to modify it, based on our experience, and to combine it with the immunohistochemical features (Table **1**). Pheochromocytoma and metastatic tumors should also

Table 1: Weiss's Modified Criteria and Immunohistochemical Parameters Used to Differentiate Adrenocortical Carcinoma form its Benign Counterpart [4, 6, 8, 12, 23]

	Parameter	Adrenocortical adenoma	Adrenocortical carcinoma (ACC)
Weiss's modified criteria	1.Diffuse architecture	absent	≥ 1/3 of the tumor
	2. Clear cytoplasm	> 1/4 of the tumor cells	< 1/4 of the tumor cells
	3.Capsular invasion	absent	present
	4. Venous invasion	absent	present
	5. Sinusoidal invasion	absent	present
	6. Mitotic count	< 5/50 HPF	> 5/50 HPF
	7.Atypical mitoses	absent	present
	8.Cytonuclear Fuhrman's grade	low (1-2)	high (3-4)
	9.Necrosis	absent	present
IHC	Ki67	negative	Usually <50%
	P53	negative	Usually >30%
	Bcl-2	negative	negative
	Cyclin D1	negative	negative

Table 2: Clinicopathological and immunohistochemical parameters used to differentiate adrenocortical carcinoma (ACC) from some malignant tumors (cc. = carcinoma; CEA = carcinoembryonic antigen; EMA = epithelial membrane antigen; HCC=hepatocellular carcinoma; IHC=immunohistochemistry; NET = neuroendocrine tumor) [5,8,14,18,19]

Parameter		Primary tumors		Metastases			
		ACC	Pheochromocytoma	melanoma	renal cell cc.	HCC	NET
Tumor size		70 grams - 4.7 kilos	usually small	usually small			
IHC	Keratin AE1/AE3	±	±	-	+	+	+
	Calretinin	+	-	±	-	+	-
	NSE	±		-	-	-	
	Synapthophysin	+	+	±	-	-	+
	Vimentin	+	-	+	+	-	-
	Inhibin	+	-	±	-	±	-
	Melan A	+	-	+	-	-	-
	EMA	±	-	-	+	+	+
	Chromogranin	-	+	-	-	-	+
	CEA	-	-	-	-	-	±
	HMB45	-	-	+	±	-	-
	S100	-	±	+	±	-	
	CD10	-	-	-	+	+	-

be excluded based on the clinico-pathological and immunohistochemical panel presented in Table **2**, although is admitted that there is no single specific marker to distinguish ACC from other primary or metastatic tumors of the adrenal gland [8, 18].

SYNCHRONOUS TUMORS

To our knowledge, twelve published papers reported synchronous tumors associated with ACC to date, such as follows: breast and rectal adenocarcinoma, ovarian and endometrial carcinoma, ovarian teratoma, testicular seminoma, ganglioneuroblastoma, osteosarcoma and rhabdomyosarcoma, papillary thyroid carcinoma, lung carcinoma and renal cell carcinoma [8, 24-34]. In our practice, we diagnosed a gastrointestinal tumor of the stomach (GIST), with benign potential, in a 71-year-old male, this association being first reported in the literature; the case presentation is in press (Gurzu *et al:* First case report of an adrenocortical carcinoma with gastric metastasis and a synchronous gastrointestinal stromal tumor of the stomach. Personal communication. In press). Although the association between GIST and other tumors are observed in about 13-25% of patients, most of the non-GIST-tumors are adenocarcinomas of the gastrointestinal tract, followed by breast, kidney, prostate, endometrial and ovarian cancers; only one adrenal adenoma and one adrenal neuroblastoma were reported to be GIST-associated to date [35, 36].

ACC can also be developed as part of inherited familial cancer syndromes, synthesized by Guerrera and Kebebew (2010) such as follows: Li-Fraumeni Syndrome (ACC + soft tissue sarcoma, osteosarcoma, breast cancer, brain tumors, leukemia, usually diagnosed under 20 years of age), familial Becwith-Wiedemann Syndrome (ACC + nephro-/hepato-blastoma, rahabdomyoosarcoma, nesideoblastosis + congenital malformations), Gardner Syndrome (ACC + gastrointestinal polyps/carcinomas, osteoma, soft tissue tumors, papillary thyroidian cancer, desmoids tumor), Multiple Endocrine Neoplasia type 1 (ACC + pituitary/parathyroid/pancreatic carcinomas, lipomas, angiomas) [29, 37, 38].

PROGNOSIS, THERAPY AND PERSPECTIVES

Open surgical adrenalectomy with complete tumor resection is the therapy of choice in resectable cases [1, 4] but postoperative or adjuvant chemotherapy is also indicated in metastatic stages, although a well-defined chemotherapeutic protocol does not exist and the therapeutic options are limited [20-22, 39]. About 80% of cases seem to receive postoperative chemotherapy [2] but the survival rate remains strongly dependent by the tumor stage, decreasing from 159 months in stages I-II until 26 and 5 months, in stages III and IV respectively [2], with a 5-year survival rate about 60% in the intra-adrenal tumors and below 30% in resectable metastatic cases respectively; the number of organs involved by the metastatic process (less or more than two tumoral organs) is a more valuable prognostic factor than the location of any involved organ [4, 39]. The biological behavior is not influenced by the microscopical subtypes ACC or Ki67 index but a mitotic rate >20/50 HPF together with a significant rate of atypical mitoses associates a very short specific survival; the benefits of loco-regional lymph node dissection and/or metastasectomy are poorly explored [4, 39]. Identification and removal of the tumor emboli from renal or inferior cava veins are mandatory.

The commonest chemotherapic drugs used in these cases are the classical ones, such as cisplatinum-based products, doxorubicin, etoposide, streptozocine, or mitotane. They can associate several side effects, such as gastrointestinal tract toxicity and neurologic disorders and the results are below expectations [1].

Mitotane, known as o,p' - DDD or (RS) - 1 - chloro - 2 - [2,2 - dichloro - 1 - (4-chlorophenyl) - ethyl] - benzene is an adrenal cortex-specific adrenolytic/ antisteroidogenic/anticortisol/anti-dehydroepiandroste-rone sulfate (DHEAS) cytotoxic agent used as the standard first line therapy of ACC but the reponse rate is about 30% [4, 20, 40]. Mitotane + adjuvant radiotherapy and also mitotane + interferon-beta are postulated to present superior benefits [39, 41]. Paclitaxel and carboplatin, without mitotane, are also used [29].

K-ras wild-type ACCs could benefit by anti-EGFR antibodies Cetuximab and/or Panitumumab but the absence of EGFR mutations [11] indicate that these drugs are not reliable to be used in these cases.

HER-2 negativity in our material also eliminated the Trastuzumab (anti-HER-2) therapeutically possibility.

Although the mTOR pathway seems to be implicated in the pathogenesis of ACC, the mTOR inhibitor rapamycin (everolimus), associated or not with mitotane, did not produce a clinical meaningful response in progressive cases [21]; whereas the mTOR inhibitor temsirolimus combined with the anti-insulin growth factor-1 receptor Cixutumumab proved

to be well tolerated with a reponse rate above 40% [22].

As we already mentioned in one of our (in press) paper, RET positivity, unreported yet in literature, could indicate a possible response of these tumors at Regorafenib, a novel oral drug that seems to be an anti-angiogenic and anti-oncogenic kinase inhibitor that acts against KIT, RET, RAF and VEGF genes [42].

Other substances were proposed in the most recent studies, such as follows: aclarubicin, an inhibitor of the TOP2A protein [43]. Their efficacy should be tested in future clinical multicenter collaborative trials. Further studies should also explore the molecular-targeted therapeutic approaches.

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Received on 02-06-2013 Accepted on 11-08-2013 Published on 21-08-2013

DOI: http://dx.doi.org/10.12974/2309-6160.2013.01.01.6