Fine Needle Aspiration Cytology of Adrenocortical Carcinoma – Case Report

Maja Mišić1, Željko Vidas2, Dinko Šk gro3, Branislav Kocman4, Biljana Jelić-Puškarić5 and Ika Kardum-Skelin5,6

1 Department of Cytology, »Dr. J. Benčević« General Hospital, Slavonski Brod, Croatia
2 Division of Urology, »Merkur« University Hospital, Zagreb, Croatia
3 Department of Medicine, »Merkur« University Hospital, Zagreb, Croatia
4 Department of Surgery, »Merkur« University Hospital, Zagreb, Croatia
5 Department of Medicine, Laboratory for Cytology and Hematology, »Merkur« University Hospital, Zagreb, Croatia
6 Zagreb University, School of Medicine, Zagreb, Croatia

ABSTRACT

A 49-year-old woman presented for hirsutism, deep voice and hypertension. Ultrasonography (US) revealed a solitary tumor mass, eight cm in size, of the right adrenal gland. Laboratory tests showed it to be a hormonally active, androgen secreting tumor (elevated testosterone level), which was consistent with the clinical picture of the disease. After histopathological analysis tumor was signed out as adrenocortical carcinoma, a low risk carcinoma according to Weiss’ classification. One year later on regular follow up, US revealed a suspicious growth measuring 65x43 mm in the projection of the lower pole of the right kidney. The finding was verified by computerized tomography and the patient was reoperated on. Exploration revealed secondary growth in the region of greater omentum, without infiltration of adjacent organs. Histopathologic analysis confirmed metastatic ACC. 8 months after the second operation and after 6 chemotherapy cycles according to EAP protocol, control CT showed enlarged para-aortic lymph nodes and a node along the upper pole of the right kidney. Cytologic puncture was performed. Cytologic opinion was recidive of primary malignant disease. ACC is a rare malignant epithelial tumor of adrenal cortical cells, with high malignant potential. Morphologically (histopathology and cytology), differential diagnosis includes adenoma on the one hand, and renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) on the other hand. A combined evaluation of clinical features, size or weight, microscopic appearance, immunohistochemical and molecular genetic data is necessary to ensure a correct diagnosis. The purpose of this case report is to present clinical and cytomorphologic features of our case of adrenocortical carcinoma which is very rare in cytology practice.

Key words: adrenal cortical carcinoma, cytology, fine needle aspiration cytology

Introduction

Adrenal cortical carcinoma is a malignant epithelial tumor of adrenal cortical cells. The incidence is about 0.1 cases per 100,000, with predilection for females. It has bimodal age distribution, with peak in first and fifth decade. Approximately half of all ACCs are hormonally functional. The most common presentation is associated with glucocorticoid (Cushing syndrome) and androgen (virilization in women) oversecretion by the tumor. Mineralocorticoids may contribute a severe state of mineralocorticoid excess with high blood pressure and hypokalaemia. A significant subset of ACCs secretes only androgens and some show no clinical features of hormone excess1. Adrenal cortical carcinomas (ACCs) tend to be large (90% are greater than 50–60 mm). Necrosis, hemorrhage and calcifications are common1,2. Displacement or involvement of adjacent organs, as well as hepatic and nodal metastases are also present frequently1. ACCs have architectural and cytological features that generally recapitulate the normal adrenal cortex. The most common architectural pattern is that of patternless sheets of cells interrupted by a fine sinusoidal network. Broad trabecule or large nests of cells may be seen. Cyto-
logically, ACCs are composed of varying numbers of cells with eosinophilic or bubbly clear cytoplasm. Nuclear atypia varies from non-existent to highly pleomorphic. Mitotic rate also varies widely. The FNA smears of ACCs are usually rich in cells. With a few exceptions, the experience with these tumors is limited to high grade malignant tumors. Therefore, in most cases the smear pattern is that of a high grade malignant tumor, whereas well differentiated tumors are rarely seen.

The smears of well differentiated tumors contain relatively uniform tumor cells, occurring either singly or in loose clusters, with abundant, eosinophilic granular cytoplasm, relatively large, often eccentric, but uniform nuclei with a coarse chromatin pattern and prominent nucleoli. Capillary vessels may be occasionally observed within the cell clusters. Foci of anisonucleosis may be observed among the monotonous population of tumor cells. The resemblance to the grade 2 or 3 granular cell variant of RCC is inescapable. Poorly differentiated cortical carcinomas yield large anaplastic malignant tumor cells of variable sizes, singly or in loose clusters. Many of the large cells are multinucleated. The nuclei are very pleomorphic and contain prominent nucleoli. Abnormal mitoses can be seen. Such smear patterns are not specific, and may be observed in any poorly differentiated tumor with giant cells. Somewhat similar smear pattern may also occur in pheochromocytoma. Immunohistochemical profiling may be helpful in separating ACCs from renal cell and hepatocellular carcinoma, adrenal medullary and metastatic tumors.

Immunoreactivity for alpha-inhibin and A 103 anti-Melan A antibody is sensitive but not specific for ACCs. ACCs are variably reported to be negative to weakly positive for cytokeratin and negative for epithelial membrane antigen, carcinoembryonic antigen and glycoprotein HMFG-2. They are negative for chromogranin A, the most reliable marker for discriminating them from adrenal medullary tumors. Other neural markers are variably positive. The major differential diagnosis is with adrenal cortical adenoma. Useful histological criteria are mitotic rate and the presence of vascular or capsular invasion. The MIB-1/Ki-67 labeling index may be of value and usually averages about 5–20%. Findings favoring metastatic carcinoma rather than ACCs include bilaterality and evidence of any glandular, squamous or small cell histology. The five-year survival rate is 50–70%.

**Case Report**

A 49-year old woman presented for hirsutism, deep voice and hypertension. The hypertension was first observed 15 years ago (200/100 mmHg) and was treated with antihypertensives and controlled regularly. Ultrasound examinations of abdomen were performed once or twice a year. 11 years ago a patient had a rupture of cerebral blood vessel aneurysm which was treated surgically. 6 years ago, an angiomyolipoma of the right kidney was discovered ultrasonographically, and confirmed by computed tomography. About half a year ago, patient noticed hirsutism of the upper and lower limbs, deep voice and

---

**Fig. 1. FNA smear of adrenocortical carcinoma (May-Grünwald- Giemsa staining, x1000):** a) noncohesive malignant large, pleomorphic cells, b) cells with polymorphic, hyperchromic, irregular nuclei, c) large nuclei with prominent nucleoli, perinucleolar halo and abundant, pale basophilic granular cytoplasm, d) mitotic figures.
higher arterial blood pressure values despite the regular antihypertensive therapy. Ultrasonography revealed a solitary tumor mass of right adrenal gland, 78x65 mm in size. An angiomyolipoma of the lower pole of right kidney was also revealed. Laboratory tests showed increased testosterone level of 24.5 nmol/L (reference value is less than 7). Total metanephrine and vanilmandelic acid levels were within normal limits. These findings suggested hormonally active, androgen secreting tumor. Surgical treatment was indicated and performed. Resected tumor tissue was paraffin-embedded and hematoxylin-and-eosin-stained slides were analyzed. After histopathological analysis tumor was signed out as adrenocortical carcinoma, a low risk carcinoma according to Weiss classification. Macroscopically, tumor was soft, yellow-brown, with areas of necrosis and hemorrhage. Histologically, tumor consisted of widely anastomosing trabecular formation with delicate, cleft-like vascular canals. However, in serial cuts, areas of irregular stripes of pleomorphic tumor cells within abundant mixoid stroma were present. More than 75% cells had eosinophilic cytoplasm, partly with polymorphic, hyperchromatic, irregular, large nuclei with mitoses (less than 5 per 10 HPF), and few atypical mitoses. Surface was covered with thin fibrous capsule, and partly with atrophic adrenal tissue. There was no clearly visible vascular invasion, but capsular invasion was found. No extension to adjacent adipose tissue and lymph nodes was observed. Immunohistochemical analysis showed vimentin, NSE, synaptophysin (+/-) positivity, and NF, chromogranin, EMA and CK (AE1/AE3) negativity. Ki-67 positivity was seen in more than 50% of tumor cells. An angiomyolipoma of the right kidney was operated and histopathologically examined at the same time.

One year later, on regular follow up US study, a suspicious growth was diagnosed in the projection of the right kidney. Computed tomography showed a homogenous, sharply demarcated tumor mass, 65x43 mm in size, in the right lower hemiabdomen between the small intestine convolutions. Surgical procedure was performed and a part of greater omentum with encapsulated tumor mass was extirpated. Macroscopically, tumor was sharply demarcated, soft, yellow-brown, with areas of necrosis. Histopathological analysis revealed diagnosis of metastatic adrenal cortical carcinoma. 8 months after second operation and 6 chemotherapy cycles according to EAP protocol, control CT showed a tumor mass, 24x20 mm in size, along the upper pole of the right kidney and enlarged para-aortic lymph node, 28 mm in greatest diameter. US guided fine needle aspiration of the tumor mass in the projection of the upper pole of the right kidney was performed. The yielded material was placed and smeared on slides, air-dried and May-Grünwald-Giemsa (MGG) stained. Cytologic analysis showed numerous large tumor cells, individual and in papillary clusters, with polymorphic, hyperchromic, irregular nuclei, prominent nucleoli with perinucleolar halo, bi- and multinucleation and abundant, homogenous, pale basophilic cytoplasm (Figures 1a-d). Tumor cells were positive for vimentin, NSE, Ki-67, synaptophysin and epithelial markers (BerEP4 and epithelial membrane antigen, Figures 2a and b). Surgical treatment and adjuvant radiotherapy of recidive was proposed. Histopathological analysis revealed diagnosis of recidivant adrenocortical carcinoma within subdiaphragmal, perirenal and paraaortal lymph nodes and VII liver segment. Tumor tissue was not found in right kidney, urether and renal artery and vein. Despite all supportive therapy the patient died.

Discussion

Virilizing adrenal carcinoma is a very rare disease. The diagnosis of ACC is often difficult, because this tumor may present with direct extension into adjacent renal parenchyma or with metastatic disease. ACC can be diagnosed by US, CT or MRI. These radiological techniques in the absence of spread cannot distinguish a malignant from benign process. Percutaneous fine needle aspiration cytology under CT or US may be useful in recurrent disease and particularly to exclude metastasis. Adrenocortical neoplasms have been divided into adenomas and carcinomas. The bias toward high grade malignant tumors in cytologic material is presumably a result of clinical case selection for FNA. Many tumors can be easily placed into one category or another, but cases exist for which the distinction is difficult and to some extent arbitrary. Adenomas tend to be smaller, more homogenous and lacking hemorrhage and necrosis. Weiss

Fig. 2. FNA of adrenocortical carcinoma, positive immunocytochemical stain (LSAB x1000) for a) NSE and b) vimentin.
listed the following microscopic criteria as a suggestive of malignancy in an adrenocortical tumor: nuclear grade III or IV, mitotic rate greater than 5 per 50 high-power fields, atypical mitoses, paucity or absence of clear cells, diffuse architecture, necrosis, capsular and vascular invasion. Immunohistochemically, adrenal cortical adenomas show a great expression of low-molecular-weight keratins and a lesser expression of vimentin that ACC. A combined evaluation of clinical features, size or weight, microscopic appearance, immunohistochemical and molecular genetic data is necessary.

The second important differential diagnosis is between ACC and renal cell carcinoma, which can invade adrenal gland. Microscopically, these two tumors resemble each other a great deal. Features favoring the diagnosis of renal cell carcinoma are the presence of glands and abundant cytoplasmic glycogen, but neither is pathognomonic. Perhaps the most important difference is cytoplasmic vacuolization which is present in RCC, but not in adrenocortical carcinoma. Immunohistochemically, strong positivity for cytokeratin, EMA, CD 10 and Lewis blood group isoantigen favors RCC. Positivity for inhibin, A103, Melan-A and synaptophysin favors ACC. The third differential diagnosis is adrenomedullary tumor which is more likely if chromogranin reactivity is present. Adrenocortical carcinoma can have overlapping histological features with hepatocellular carcinoma. Staining for inhibin and Melan-A is observed in adrenal cortical tumors but not in HCC. Inhibin is expressed in around 70% of adrenocortical carcinomas and Melan-A in 50–60%. The sensitivity can be improved to more than 80% by combination of both antibodies. Also, CEA is not expressed in adrenocortical carcinoma. Most adrenocortical tumors are negative for keratin while hepatocellular carcinoma is positive for CK 8 and CK 18.

**Conclusion**

ACC is a rare tumor of high malignant potential, deriving from adrenal gland cortex. Morphologically (histopathology and cytology), there is the problem of differential diagnosis from adenoma on the one hand, and from renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) on the other hand. Proliferation markers such as Ki67 or DNA-ploidy help differentiate ACC from adenoma, and cellular markers (alpha-fetoprotein, CD10, RCC marker, vimentin, EMA, keratins 7 and 20, alpha-inhibin, and polyclonal antibodies against carcinoembryonic antigen (pCEA)) from RCC and HCC.

**REFERENCES**


M. Mišić «Dr. J. Benčević» Department of Cytology, General Hospital, A. Štampara 42, 35 000 Slavonski Brod, Croatia e-mail: maja.misic1@gmail.com

**CITOLOŠKA SLIKA KARCINOMA NADBUBREŽNE ŽLIJEZDE: PRIKAZ SLUČAJA**

**SAŽETAK**

Adrenokortikalni karcinom (ACC) je maligni epitelni tumor stanica kore nadbubrežne žlijezde. Polovina svih ACC-a su hormonski aktivni. Kod 49 godišnje bolesnice zbog pojačane dlakavosti, dubljei glasa i hipertenzije ultrazvučnom (US) obradom je nađena solitarna tumorska tvorba desne nadbubrežne žlijezde veličine 8 cm. Laboratorijskom obrazułu utvrđeno je da je tromba radi hormonski aktivnog tumoru koji luči androgene (povišena vrijednost testosterona) u što se uklapa i klinička slika bolesti. Patohistološka analiza ukazala je na postojanje adrenokortikalnog carcinoma (ACC) koji prema Weissovoj klasifikaciji spada u «low risk» karcinom. Na redovnom US pregledu godinu dana kasnije dijagno...
stirana je tvorba (65x43 mm) u području donjeg pola desnog bubrega. Nalaz je potvrđen i kompjuteriziranom tomografijom te se ponovno pristupilo operativnom zahvatu. Eksploracijom se nade sekundarizam u području velikog omentuma koji ne infiltrira priležeće organe. Patohistološka dijagnoza je odgovarala metastatskom ACC. Nakon 6 ciklusa kemoterapije po EAP protokolu i 8 mjeseci iza drugog operativnog zahvata prisutni su povećani paraortalni limfni čvorovi i čvor uz gornji pol desnog bubrega, koji je citološki punktimiran. Citološki nalaz govorio je u prilog recidiva osnovne maligne bolesti. ACC je rijedak tumor visokog malignog potencijala. Morfološki (histopatološki i citološki) pojavljuje se diferencijalno dijagnostički problem prema adenomu s jedne strane i karcinomu bubrega i hepatocelularnom karcinomu s druge strane. Potrebna je kombinirana evaluacija kliničkih pokazatelja, veličine ili težine tumora, mikroskopskog izgleda, imunohistokemijskih i molekularnih genetičkih podataka. Svrha ovog članka je prikaz kliničkih i citomorfoloških osobitosti našeg slučaja karcinoma kore nadbubrežne žlijezde koji je vrlo rijedak u citološkoj dijagnostici.