

Disseminated adrenocortical carcinoma: case report

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Abstract: Adrenocortical carcinoma is a rare neoplasm occurring with a frequency of 1–2 cases per million. It is characterized by significant malignancy with the mean survival of about 28 months, and in the presence of documented metastases survival is shorter up to 8 months. This type of a tumor is slightly more frequent in women (58.6%) than in men (41.4%). Etiology of adrenocortical carcinoma is still unclear, but a role of genetic and environmental factors has been largely considered. Most of the carcinomas (60%) are functional and usually the first manifestation is Cushing's syndrome with virilization. The tumor size is still the best single predictor of prognosis. Histopathology specimen from biopsy or obtained during operation should be stained for Melan A, which can confirm the adrenal origin of the tumor. The only method of treatment is a complete surgical excision of the carcinoma. However, because of its dynamics, metastases cannot be reliably excluded. We present the case of functioning adrenocortical cancer in a 37-year-old patient who at the time of diagnosis had 12 cm in diameter tumor of the left adrenal gland and metastases to the liver and lung. In the article the symptoms associated with hormones produced by the carcinoma, diagnostics and treatment with regard to the progression of the disease have also been discussed.

Key words: adrenocortical carcinoma, cortisol, metastases, mitotan

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The 37-year-old patient with the 3-month-long history of hypertension came to the S. Żeromski Hospital in Kraków because of an increasing edema of his lower right limb accompanied by reddening of the skin and pain. On admission to hospital the patient was examined by a surgeon, who diagnosed inflammation of the right knee joint. Because of high hypertension (200/100 mmHg) and tachycardia (120/min) the patient was admitted to the Department of Internal Medicine.

Before hospitalization he obtained enalapril 2×5 mg/24 h because of hypertension.

The blood examination revealed potassium 3.38 mmol/l, increased levels of aspartate (AST) – 87 U/l and alanine aminotransferase (ALT) – 125 U/l, hyperglycemia – 7.72 mmol/l, C-reactive protein (CRP) – 54 mg/l and a slightly decreased level of total serum proteins – 51.8 g/l. Morphology, blood coagulation parameters, the erythrocytes sedimentation rate, serum sodium, bilirubin and renal parameters remained in a normal range.

Angiotensin-converting enzyme inhibitor, calcium channel blocker, β -blocker, and potassium sparing diuretics were added to the treatment. It resulted in the blood pressure decrease to 160/90 mmHg.

Despite the previous oral and later intravenous potassium supplementation to 80 mEq/24 h, potassium level decreased and on the 11th day of hospitalization it was 2.24 mmol/l. The twenty-four hours urine potassium excretion was in a normal range.

Chest X-ray revealed a soft, spotted, round shadow with a diameter of 17 mm in the middle left lung field and cardiac enlargement in a transverse dimension.

The abdominal USG examination of the upper pole of the right kidney showed a solid tumor $12 \times 10 \times 10$ cm in size and numerous metastases in the liver.

The initial diagnosis was a renal carcinoma with metastases to the liver and lungs. In order to verify the above diagnosis the abdominal computed tomography (CT) was performed. The solid, slightly vascularized tumor $20 \times 16 \times 11$ cm in size in the left adrenal gland and numerous metastases in the liver was confirmed. Other organs remained unchanged (Fig. 1 and Fig. 2).

Because of the suspicion of the left adrenal gland carcinoma the patient was directed to the Department and Clinic of Endocrinology, Collegium Medicum of the Jagiellonian University in Kraków for further diagnosis and treatment.

On admission to the Clinic the physical examination revealed changes on the trunk and the skin of upper and lower extremities in the form of irregular red-wine spots, facial flush and the Cushing constitution. The mean value of blood pres-

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Fig. 1. Computed tomography of abdomen. Left adrenal gland tumor

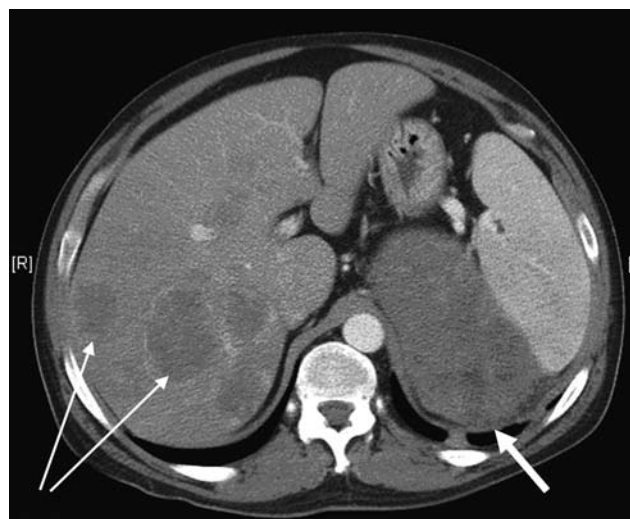


Fig. 2. Computed tomography of abdomen. Left adrenal gland tumor (thick arrow) with numerous metastases to the liver (narrow arrows)

sure was 150/90 mmHg. The electrocardiogram showed a sinus rhythm of 90/min and T-wave inversion in I, II, aVL, aVF leads.

The blood examination revealed serum potassium 2.7 mmol/l levels, increased levels of AST – 137 U/l and ALT – 218 U/l, hyperglycemia – 7.72 mmol/l, CRP – 54 mg/l and a slightly decreased level of total serum proteins – 51.8 g/l. Morphology, blood coagulation parameters, serum sodium, bilirubin, amylase, total serum proteins, albumin, and renal parameters remained in a normal range. Cortisol value in the daily rhythm were high and rigid (Tab. 1).

Because of low values of serum potassium the central venous catheter was inserted and intravenous potassium 10 mmol/h

was administrated. Although all typical groups of hypotensive drugs were used the values of blood pressure were 200/110 mmHg.

Glycemic profile showed postprandial hyperglycemia in the afternoon. Diabetic diet and one short-acting insulin injection (4 units) at 3 pm were introduced. Good control of glycemia was obtained.

Inhibitor of steroidogenesis (aminoglutetimide) in a dose of 2 g/24 h was added to the therapy. On the third day after its inclusion to the therapy a decrease in blood pressure was observed. On the 5th day blood pressure normalized to 140/80 mmHg and a gradual reduction in hypotensive drugs was tested.

Serum potassium levels also normalized, which allowed only oral potassium supplementation. Seven days after aminoglutetimide inclusion to the therapy, levels of cortisol decreased, which correlated with improvement of the patient general state (Tab. 2).

To complete adrenal gland function assessment, 24 hours urine metoxycatecholamine and aldosterone collections were obtained. Results remained within a normal range.

Right liver lobe metastasis biopsy revealed malignant cells. The carcinoma cells showed the expression of Melan A. Reactions for epithelial membrane antigen and inhibin were negative.

The final diagnosis was: a functional left adrenal gland carcinoma with metastases to the liver and the left lung.

Mitotane was added to the therapy in a dose of 6 g/24 h. At the same time due to normalization of blood pressure, cortisol and electrolyte levels inhibitor of steroidogenesis were withdrawn. One week later an increase in blood pressure and a decrease in potassium levels were observed. Aminoglutetimide in a dose of 2 g/24 h was introduced again. Five days later cortisol levels decreased below the reference range. To protect the patient against adrenal insufficiency hydrocortisone in a dose of 20 mg/24 h was substituted. At the same time aminoglutetimide was reduced to a dose of 750 mg/24 h.

In order to qualify the patient to the surgery procedure the abdominal USG was performed. The examination was carried out 1 month after the abdominal CT and 2 weeks after the introduction of mitotane to the therapy. The ultrasonography showed a significant progression of the disease: the whole right liver lobe was massively metastatic. The left liver lobe contained solitary metastases with diameters of up to 67 mm. The main tumor was polycystic and slightly vascularized. It spread to the tail of pancreas, right kidney, spleen and its vein, and modulated left kidney vessels. Its distance from the aorta was 5 mm.

Because of the disease extension, the patient was disqualified from surgery. In the case of the tumor size regression after mitotane, surgery to reduce the tumor mass was considered.

The somatostatin receptor scintigraphy (99mTc-Edda/HYNIC/TATE) was performed. Neither in the tumor nor in metastases receptors for somatostatin were detected.

After 5 weeks of hospital treatment the patient was discharged in a stable state without pain, with normal potassium

Table 1. Levels of cortisol on admission to hospital (November 8, 2006)

Hour	6:00	10:00	18:00	22:00
Level of cortisol (norm 2.9–22.9 µg%)	61.55	62.87	62.39	57.24

level values and blood pressure not exceeding 150/90 mmHg. The therapy with mitotane 6 g/24 h, aminoglutetimide 750 mg/24 h, hydrocortisone 20 mg/24 h was maintained. Also angiotensin-converting enzyme inhibitor, α -blocker and oral potassium supplementation was continued.

Three weeks later and two months after the beginning of mitotane use the follow-up abdominal USG was performed. The examination showed diminishing of the tumor size to 10 × 10 × 9 cm and lack of infiltrating to right kidney pancreas. The metastases to the liver were still numerous but a positive response to mitotane was shown.

The Cushing constitution and lower extremities edemas up to knee joints were still present. The mean blood pressure was 130/70 mmHg.

Follow-up parameters were: potassium – 5.6 mmol/l, sodium – 134 mmol/l, AST – 564 U/l, ALT – 205 U/l, international normalized ratio – 1.23, activated partial thromboplastin time – 38 s, total serum proteins – 56 g/l, urea – 9.9 mmol/l, creatinine – 128 µmol/l, Hb – 10.9 g%.

A decision about operation was made, but because of the extent of changes in the liver the consulting surgeons abided by it. Mitotane 6 g/24 h and aminoglutetimide 750 mg/24 h therapy was continued. Three weeks another follow-up abdominal USG was performed. The significant progression of the disease was observed. The tumor grew to 14 cm in diameter and almost the whole liver was destroyed.

The patient died 3 months after the diagnosis and 2.5 months after the beginning of mitotane use. The death was caused by a severe renal insufficiency due to the tumor lysis syndrome.

DISCUSSION

We presented the case of disseminated adrenocortical carcinoma, that is a rare neoplasm occurring with a frequency of 1–2 cases per million. It is characterized by significant malignancy and poor prognosis: mean survival is about 28 months, and in the presence of documented metastases survival is shorter up to 8 months. Etiology of adrenocortical carcinoma is still unclear. A role of genetic and environmental factors e.g. pesticide pollution, has been largely considered [1].

Most of the carcinomas (60%) are functional; about 30% produce cortisol, 20% androgens, 10% estrogens and 2% aldosterone. Usually its first manifestation is Cushing's syndrome with virilization [2].

Symptoms of a nonfunctional cancer are connected with the local mass effect, e.g.: a feeling of fullness in the stomach, nausea, vomiting, digestive disorders [3,4]. In rare cases its first manifestations are distant metastases, e.g. to bones, which can

Table 2. Levels of cortisol during treatment (November 16, 2006)

Hour	6:00	18:00
Level of cortisol (norm: 2.9–22.9 µg%)	23.43	24.86

cause pathological fractures or bone pain [5].

Dehydroepiandrosterone (DHEA) can be used as a marker of malignancy. Its increased level suggests adrenocortical cancer, whereas a normal level suggest benign tumor.

The tumor size is still the best single predictor of prognosis. The recommended imaging exams are CT and magnetic resonance (MR) equally, but the MR is more sensitive. Routine adrenal biopsy is not recommended, because of the procedure risk and a limited diagnostic value. Histopathological specimen from biopsy or obtained during operation should be stained for Melan A, which confirms the adrenal origin of the tumor [6]. In this case because of the tumor extent and liver metastases, biopsy was obtained to confirm the diagnosis.

The only one effective method of treatment is a complete tumor excision. The majority of cases are diagnosed when distant metastases are present, which makes prognosis even worse.

Mitotane is the first choice pharmacological treatment of adrenocortical carcinoma. It is used independently of the stage of the disease, because the presence of micrometastases can never be excluded. In the case of a local cancer (without crossing adrenal's capsula) a mitotane daily dose is up to 4 g. When a cancer infiltrates nearest tissues or metastases to lymph nodes are present, a daily dose increases to 4–8 g. A dose of 4–10 g daily is recommended when distant metastases are diagnosed. After about one month of treatment the therapeutic action of mitotane reveals [7]. Monitoring of drug levels in blood, which should be over 14 mg/l, is recommended. Mitotane treatment in the local disease should last 3–5 years. In the case of regional or distant metastases there are no time limits for mitotane treatment.

Mitotane causes numerous side effects, e.g.: pancytopenia, the growth of aminotransferases, consciousness disturbances and myasthenia, mainly dysarthria. Prednisolone in a daily dose of 5–10 mg is used to alleviate symptoms.

Mitotane may also inhibit adrenal glands activity; therefore hydrocortisone in a daily dose of 40–60 mg as a substitution is required. Physiological cortisol rhythms should be maintained, thus the morning dose should be higher than the afternoon one.

In the presented case mitotane decreased the tumor size but did not decrease the level of cortisol. After aminoglutetimide treatment the decrease in cortisol level was so sharp that

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the substitution of hydrocortisone was required (20 mg per day). Low levels of potassium or high blood pressure can be connected with an unsuccessful therapy (too low drug dose) or with the progression of the disease.

Chemotherapy is used in the case of regional or distant metastases presence. Usually cisplatin, etoposide or doxorubicin are used [1,8,9]. If mitotane therapy is unsuccessful, cytotoxic chemotherapy is possible, but its efficacy is much lower (23% of partial and 4% of total remissions).

Radiotherapy treatment in adrenocortical cancer requires further medical research [10].

The time from the beginning of mitotane therapy to the appearance of its first effects can be long, therefore in the cases of functional adrenocortical cancers, inhibitors of steroidogenesis are required. Inhibitors of 11 β hydroxylase, like metyrapone, ketoconazole, etomidate or glutatimide can be used. The main side effect of this treatment is adrenal glands insufficiency, which requires the substitution.

Frequent follow up visits and examinations are necessary after adrenalectomy. Only early diagnosis of relapse gives the chance of a successful re-operation. After adrenalectomy the follow-up abdominal and chest CT should be performed every 3–4 months for the first two years. Later the CT exams can be performed less often. The follow-up of DHEA levels may be useful as a relapse marker in the case of adrenocortical cancer. Its increased level can be detected even long before the confirmation of the disease relapse on imaging examinations. Regardless of the adrenocortical cancer treatment, prognoses for patients remain poor. But like in other malignant neoplasm cases early diagnosis increases the chances of long time survival. Therefore, in the cases of hypertension resistant to a typical hypotensive therapy, especially in young people with no familial history of the disease, secondary hypertension, also resulting from adrenal gland disorders, should be considered in the diagnostics.

REFERENCES

1. Szczekliki A, ed. *Choroby wewnętrzne*. Tom 1. Kraków, Medycyna Praktyczna, 2006; 1143.
2. Tupikowski W, Tupikowska-Bednarek G, Florczak A. Adrenocortical carcinoma and its treatment. *Postępy Hig Med Dośw*. 2004; 26: 27-36.
3. Samaan NA, Hickey RC. Adrenal cortical carcinoma. *Semin. Oncology*. 1987; 14: 292-296.
4. Dackiw AP, Lee JE, Gagel RF, Evans DB. Adrenal cortical carcinoma. *World J Surg*. 2001; 25: 914-926.
5. Kasperlik-Zaluska AA, Migdalska BM, Makowska AM. Incidentally found adrenocortical carcinoma. A study of 21 patients. *Eur J Cancer*. 1988 34, 1721-1724.
6. Fassnacht M, Hahner S, Polat B, et al. Efficacy of adjuvant radiotherapy of tumor bed on local recurrence of adrenocortical carcinoma. *J Clin Endocrinol Metab*. 2006; 91: 4501-4504.
7. Podlewski J, Chwalibogowska-Podlowska A. *Leki współczesnej terapii*. Warszawa, WL PZWL, 1994; 591-592.
8. Lazaro Santander R, Adnres Gozalbo C, Cortes Vizcaino V, et al. Low grade onco-cytic adrenal carcinoma. *Arch Esp Urol*. 2001; 54: 1123-1126.
9. Assie G, Antoni G, Tissier F, et al. Prognostic parameters of metastatic adrenocortical carcinoma. *J Clin Endocrinol Metab*. 2007; 92: 148-154.
10. Kopf D, Goretzki PE, Lehnert H. Clinical management of malignant adrenal tumors. *J Cancer Res Clin Oncol*. 2001; 127: 143-155.