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A place for adjuvant mitotane treatment in low-risk patients with adrenocortical carcinoma – case report

Miejsce dla uzupełniającego leczenia mitotanem u pacjentów niskiego ryzyka z rakiem kory nadnercza – opis przypadku

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S u m m a r y

We present a case of a 56-year-old women treated for hypertension with tumor of adrenal gland confirmed on CT in 2006, sized 16 x 18 mm with pre-contrast density about 30 Hounsfield Units. She hadn't decided to undergo further evaluation and only the ultrasound of the abdomen was performed annually for four years. In 2010, as soon as enlarging of the mass was revealed, the clinical evaluation was performed which led to suspicion of adrenocortical carcinoma. The patient underwent margin-free complete laparoscopic resection of the tumor (R0) and was classified as stage I (ENSAT) adrenocortical carcinoma with low-risk of recurrence (Ki-67 index < 10%, resection status R0). According to current clinical oncological guidelines, she was not administered adjuvant mitotane from oncologist. The treatment started two months later, but it was four years after the tumors had been found. Two years after the surgery metastases occurred, and one year later the patient died. There is high probability of existing occult micrometastases at the time of diagnosis even in patients with low-risk and low stage of the disease. The data obtained from several studies indicate that such patients may benefit from administering adjuvant mitotane. Delay in treatment with mitotane may lead to faster recurrence of ACC and worsen the survival, as happened to the presented patient. Results of the first prospective, randomized trial (ADIUVO trial) are expected in 2014. They will hopefully lead to unified recommendations in low-risk patients with stage I or II of the disease.

Key words: adrenocortical carcinoma, adrenal cancer, mitotane

S t r e s z c z e n i e

Przedstawiamy przypadek 56-letniej kobiety leczonej z powodu nadciśnienia tętniczego z guzem prawego nadnercza potwierdzonym w badaniu TK jamy brzusznej w 2006 roku wielkości 16 x 18 mm i gęstością przed podaniem kontrastu wynoszącą 30 j. Hounsfielda. Pacjentka nie zdecydowała się na dalszą diagnostykę i przez cztery kolejne lata co roku przeprowadzano jedynie badanie ultrasonograficzne jamy brzusznej. W 2010 roku, gdy stwierdzono powiększanie się guza, przeprowadzono ocenę kliniczną, a następnie wysunięto podejrzenia raka kory nadnercza. Chora przebyła całkowitą resekcję guza (R0); stadium zaawansowania nowotworu (wg klasyfikacji ENSAT) określono jako I, z niskim ryzykiem nawrotu choroby (Ki-67 index < 10%, doszczętność zabiegu R0). Zgodnie z obowiązującymi wytycznymi dla leczenia onkologicznego pacjentka nie otrzymała uzupełniającej chemioterapii mitotanem. Leczenie rozpoczęto dwa miesiące później, ale było to cztery lata po pierwszym zobrazowaniu guza. Dwa lata po operacji pojawiły się przerzuty odległe i rok po wznowie nowotworu pacjentka zmarła z powodu progresji choroby. Istnieje bardzo duże prawdopodobieństwo istnienia ukrytych mikroprzerzutów w momencie diagnozy nawet u pacjentów z niskim stopniem zaawansowania i niskim ryzykiem nawrotu choroby. Dane uzyskane z licznych badań wskazują na korzyści z wczesnego włączania mitotanu w tej grupie pacjentów. Opóźnione leczenie może prowadzić do szybszego nawrotu i pogarszać przeżycie, tak jak u opisanej pacjentki. W 2014 roku spodziewamy się wyników pierwszego, prospektywnego, randomizowanego badania klinicznego nad rakiem kory nadnerczy (ADIUVO); miejmy nadzieję, że pozwolą one na sformułowanie jednolitych zaleceń dotyczących postępowania u pacjentów z niskim stopniem zaawansowania choroby (I lub II) i niskim ryzykiem nawrotu choroby.

Słowa kluczowe: rak kory nadnerczy, mitotan

CASE REPORT

A 56-year-old woman was referred to Endocrinology Clinic in September 2010. She was treated for severe hypertension from 2006. The values of blood pressure were up to 220/170 mmHg. In the same year, ultrasound of the abdomen revealed tumor in the right

adrenal gland, which was confirmed on CT, size about 16 x 18 mm with density about 30 Hounsfield units (HU) on unenhanced scans (fig. 1). At the time, patient did not decide to undergo further examination. After that the ultrasound of the abdomen was performed every year and in march 2010 there was found, that size of the mass increased to 26 x 19 mm. For this reason and due to unstable hypertension, in June 2010 she was hospitalized in Cardiology Clinic first and then in Endocrinology Clinic, where the diagnostic evaluation was performed. Physical examination revealed some signs of Cushing's syndrome such as the "moon" face (observed by the patient within the previous six months) and enlarged fat pads in the supraclavicular fossae. Laboratory evaluation showed impaired glucose tolerance, high cortisol and low ACTH concentrations, lack of post-dexamethasone cortisol suppression, normal levels of androgens and increased levels of β-HCG. The CT scanning revealed the adrenal mass size 46 x 26 mm and contrast washout ranged from 35 to 65%. Imaging phenotype of the tumor on MRI was also not typical for adenoma and it indicated on carcinoma. Chest CT and PDG PET/CT did not reveal any positive lymph nodes or metastases. The patient was immediately treated with ketoconazole. The laparoscopic right adrenalectomy was performed three weeks after admission to the hospital. The histopathological examination revealed malignant adrenal tumor sized 35 x 30 x 50 mm and confirmed the diagnosis of carcinoma. The total score of the microscopic Weiss criteria, modified by Aubert, assessing the likelihood of malignancy, were 4 out of 7 points (> 5 mitoses/50 high power fields – 2 pts; < 25% clear tumor cells in cytoplasm – 2 pts). The necrosis, capsular invasion, abnormal mitoses were not present (0 pts) (1, 2). The threshold for malignancy was 3 points. Ki-67 proliferation index was 3-4%. In the TNM (WHO/International Union Against Cancer/the American Joint Commision on Cancer-UICC/AJCC) (3) and in the European Network for the Study of Adrenal Tumors (ENSAT) staging system (3) the patient was classified as stage I (staging systems are presented in table 1. European Society of Medical Oncology recommends the TNM system proposed by ENSAT as it seems to be predicting the prognostic stratification better than UICC system) (4, 5).

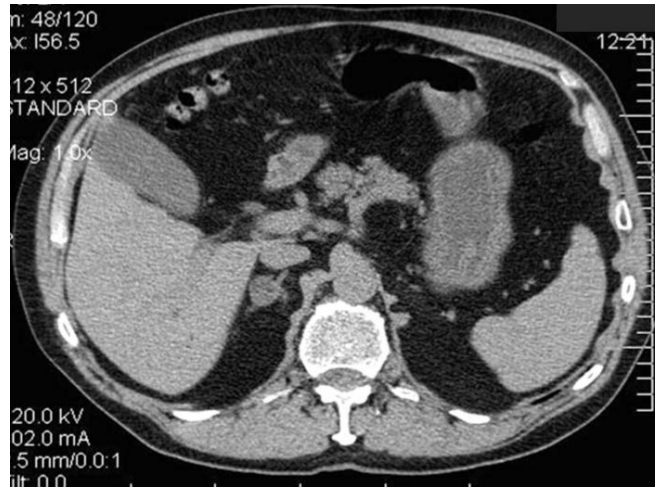

Fig. 1. Small, less than 2 cm, homogenous but with high density, tumor of right adrenal gland.

For this reason, and according to current recommendations (4, 6), the patient was not administered adjuvant mitotane from oncologist. However, when we first met the patient in September 2010, two months after surgery, she was immediately administered mitotane in dose 1.5 g a day. The dose was increased every two weeks up to 5 g a day. Concentration > 14 μg/dl was reached after 2 months, then the dose was lowered to 2-3 g a day which was enough to maintain the therapeutical concentration. Apart from hydrocortisone, suplementation of thyroid hormones was also necessary as the hypothyroidism occurred. DHEA-S and androstendion levels were below the detection limits. The patient was regularly checked for cancer recurrence and in October 2012 (2 years after diagnosis) the MRI and X-ray of the spine, performed because of the back pain, revealed metastases in the lumbar vertebrae (L3, L4) with pathological fracture of vertebral body L3 (fig. 2). The patient underwent resection of the metastases and the following radiotherapy of the spine. Five months later further imaging revealed disease progression: metastases in liver (fig. 3), bones and lungs. Because previous radiotherapy resulted in complications including anemia, leukopenia and diarrhea, the patient was disqualified from systemic chemotherapy and mitotane alone was continued. She remained under care of hospice and died 3 years after initial diagnosis.

Table 1. Staging systems for adrenocortical cancer: T1 – tumor 5 cm or less; T2 – tumor greater than 5 cm; T3 – any size with local invasion; T4 – any size with invasion of adjacent organs (by ENSAT – also venous tumor thrombus in vena cava or renal vein); N0 – no positive lymph nodes; N1 – metastasis in regional lymph node; M0 – no distant metastasis; M1 – distant metastasis (3).

TNM (UICC/WHO)				ENSAT	5-year-survival rate (5)	% of patients at the time of initial presentation (5)
Stage I	T1	N0	M0	T1, N0, M0	82	5.6
Stage II	T2	N0	M0	T2, N0, M0	58	42.3
Stage III	T1-T2 T3	N1 N0	M0 M0	T3-4, N0, M0 –	55 –	16.1 –
Stage IV	T3 T4 T1-T4	N1 N0-1 N0-1	M0 M0 M1	Any M1 – –	18 – –	36.1 – –

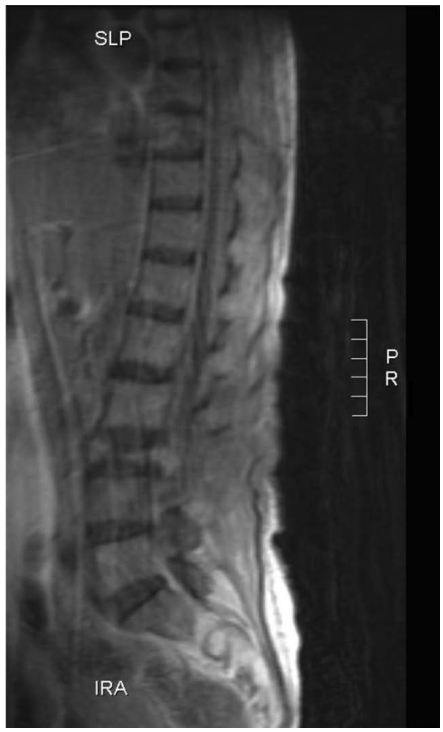

Fig. 2. MRI: compression of L3 vertebral body, caused acute back pain. On the upper parts of visualized area deformations of Th7-Th9 had been also visualized.

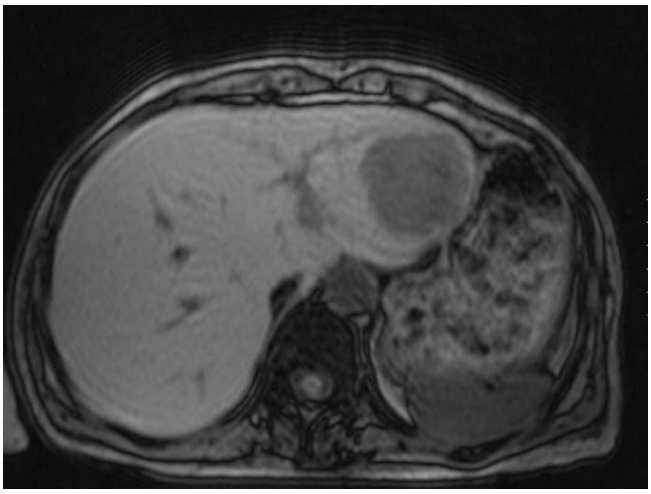

Fig. 3. MRI: 5 cm metastasis in the left liver lobe (segment II).

COMMENTS

Adrenocortical carcinoma is a rare, highly-aggressive, malignant tumor. Its incidence is estimated as one up to two per million, more frequent concerning women between 4th-5th decade of life (4). Most ACCs (about 60%) are hormone-secreting tumors with biochemical presentation of the ACTH – independent Cushing's syndrome alone, both Cushing's and virilization syndrome, virilization alone and very rare hyperaldosteronism and feminization (7, 8). All patients with an adrenal mass should undergo imaging and hormonal evaluation as recommended by ACC working group of ENSAT (4, 9). After delayed diagnostic evaluation our presented patient was suspected of having adrenocortical carcinoma and underwent margin-free complete laparoscopic resection of the tumor (R0) (4). Although open adrenalectomy is still a standard approach in ACC, recent studies show that in patients with stage I, II or tumor size less than 10 cm, there was no difference in outcomes comparing the mentioned two methods (10, 11). In addition, data from the German registry shows that standard lymphadenectomy may be beneficial in terms of long-term survival (12). Because the results were not analyzed for subgroups of different staging, it is not known if everyone, who undergo lymphadenectomy, would benefit from such standard approach.

The adjuvant radiotherapy is now recommended only for patients with incomplete or uncertain resection (R1, Rx) and for patients with stage III disease (13) although there are promising data from retrospective series of 14 patients with stage I-III showing that this method may lower the probability of local recurrence (14).

The adjuvant therapy with mitotane is the basic method to treat patients with inoperable, incompletely resected, metastatic or recurrence disease. It is also recommended for patients with complete resection (R0) and high risk of recurrence (stage III, Ki-67 > 10%) (4) and/or when tumor is larger than 8 cm (9). The outcomes of a large, international randomized trial (FIRM-ACT) indicating the beneficial role of etoposide/doxorubicin/cisplatin plus mitotane (EDP-M) lead to new standards in treatment of advanced ACC (15). However the question remains, which therapy should be performed in patients with low risk of reccurence. The presented patient was classified as stage I disease (small tumor size – 5 cm, no local invasion, no positive lymph nodes, no distant metastases) as well as a low risk patient (Ki-67 index < 10%, resection status R0). According to the European Society of Medical Oncology (4) and to the statement of international panel of experts the adjuvant mitotane therapy is not considered mandatory in such patients (6). However, although the initial complete resection of ACC is potentially curative, the recurrence of the disease is highly probable (13). In a series of 202 – patients of stage I-III disease, 40% of them developed metastases within 2 years, including 27 and 46% of patients with stage I and II disease, respectively (16). The data from retrospective analyses of 177 patients with completely resected tumor (stage I to III disease) in Italy and Germany indicate improved survival in a cohort of patients who received mitotane comparing with those who did not (17). Similar results were published from the German registry (18). The results of this report concerning 149 patients with stage II ACC indicated that those treated with mitotane had better five-year survival (87%) compared with patients who did not receive such treatment (53%) (18). Taking into consideration the presented data several centers (including ours) recommends administering mitotane to all patients with ACC immediately after surgery (13, 19) and sometimes even before the operation. There is high probability of existing occult micrometastases at the time of diagnosis even in patients with estimeted

low-risk and low stage of the disease. Delay in treatment with mitotane may lead to a faster recurrence of ACC and worsen the survival. The case reported above id the best example illustrating such statement. The therapy started 2 months after the surgery, however it was actually 4 years after the tumor had occurred.

Currently there is one prospective, international, randomized trial in progress testing the efficiacy of mitotane in low-risk patient with stage I or II of adrenal cancer (ADIUVO trial). Results of this trial are expected in 2014 (13). They will hopefully lead to unified recommendations in such patients.

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