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Embolization in an Adrenocortical Carcinoma as Palliative Therapy

R. Forstpointner[a] R. Braunschweig[b] H. Meißner[c] N. Lang[a] M. Kühl[d] A. Schalhorn[a]

[a] Medizinische Klinik III,
[b] Institut für Radiologische Diagnostik und
[c] Institut für Pathologie der Ludwig-Maximilians-Universität München
[d] KH-Zweckverband Kaufbeuren

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Summary
Background: With an annual incidence of 0.2% of new cases per 100,000 inhabitants, adrenocortical carcinoma is rare. In advanced tumor only palliative treatment modalities are practicable. Because of scarcity of the tumor, standard treatment has not been defined. The decision on therapy frequently depends on the individual situation. Tumor embolization and chemotherapy are amongst the possible options. ***Patient and Methods:*** We report on a case of a 32-year-old female patient with a large-volume hormonally active adrenocortical carcinoma and hematogenous liver metastases. This carcinoma was confirmed histologically by means of liver biopsy. Owing to the large tumor extent and metastatic spreading and also in view of the poor general condition of the patient, curative surgical therapy was not possible. For this reason, a local approach was chosen primarily with transarterial tumor embolization at the capillary level. Systemic chemotherapy was given afterwards. ***Results:*** Improvement of the patient's general condition, especially the pronounced pain symptoms, could be achieved for a short time by the embolization: both, the patient's clinical condition and the laboratory test parameters improved. However, a rapid tumor progression occured under chemotherapy, which was started after embolization. ***Conclusion:*** In advanced adrenocortical carcinoma, tumor embolization can lead to a stabilization of the disease and improvement of the symptoms as appraised by palliative criteria in some patients.

Zusammenfassung
Hintergrund: Das Nebennierenrindenkarzinom zählt mit einer jährlichen Inzidenz von 0,2% Neuerkrankungen pro 100.000 Einwohnern zu den seltenen Malignomen. In fortgeschrittenen Tumorstadien und bei chirurgisch nicht resektablen Tumoren kommen nur palliative Therapieansätze zum Einsatz. Aufgrund geringer Fallzahlen liegen wenige Studien und somit keine Standardtherapieverfahren vor. Die Therapieentscheidung richtet sich häufig nach der individuellen Einzelsituation, wobei Tumorembolisation und Chemotherapie zu den möglichen Optionen zählen. ***Patient und Methoden:*** Wir berichten über den Fall einer 32jährigen Patientin mit einem großvolumigen, hormonaktiven Nebennierenrindenkarzinom und hämatogener Lebermetastasierung. Das Karzinom wurde histologisch mittels Leberbiopsie gesichert. Aufgrund der großen Tumorausdehnung, der Metastasierung und des schlechten Allgemeinzustandes der Patientin war eine kurative chirurgische Therapie nicht möglich. Deshalb wurde primär mit der transarteriellen Tumorembolisation auf Kapillarebene ein lokales Vorgehen gewählt. Im Anschluß erfolgte eine systemische Chemotherapie. ***Ergebnisse:*** Durch die Embolisation ließ sich klinisch und laborchemisch für kurze Zeit eine Besserung des Allgemeinbefindens, insbesondere der ausgeprägten Schmerzsymptomatik, erzielen. Dieser deutlich nachweisbare Effekt ist auch histopathologisch belegbar. Ein erneuter, rascher Tumorprogreß konnte auch durch die dann eingeleitete systemische Chemotherapie nicht mehr beeinflußt werden. ***Schlußfolgerung:*** Bei fortgeschrittenem Nebennierenrindenkarzinom kann die Tumorembolisation unter palliativen Gesichtspunkten zu einer Krankheitsstabilisierung und Besserung der Beschwerden einzelner Patienten führen.

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Fax +49 761 4 52 07 14
E-mail kargergmbh@aol.com
www.karger.com

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Dr. med. Roswitha Forstpointner
Medizinische Klinik und Poliklinik III
Klinikum Großhadern
Marchioninistraße 15, D-81377 München (Germany)
Tel. +49 89 70 95-22 07
E-mail Roswitha.Forstpointner@med3.med.uni-muenchen.de

Introduction

Adrenal cortical carcinomas are rare tumors, with an estimated annual incidence of 0.5–2 / 1 million population [1]. In principle, functional and nonfunctional tumors can be distinguished. Accordingly the clinical symptoms depend on the differentiation of the adrenocortical function (e.g. Cushing's syndrome and primary hyperaldosteronism, hirsutism, virilization or feminization).

Life expectancy of patients is short and depends on the tumor stage at diagnosis. The poor prognosis can be improved by early diagnosis and radical primary operation. According to De Vita et al. [2], most patients (70%) present in the advanced tumor stage III or IV at diagnosis, i.e. they show a tumor with local infiltration and/or positive lymph nodes or additional metastatic spreading.

In principle, the primary options for treatment comprise local measures such as surgery [3, 1, 4] as the sole possibility of cure, embolization [5, 6], and local radiation [7]. In locally very advanced disease and metastatic spreading, systemic treatment such as antihormonal therapy or chemotherapy may be used for palliative purposes.

We report a patient with advanced, metastasized adrenal cortical carcinoma and a prominent symptomatology as defined by a very pressure-dolent abdomen and the possibility of tumor embolization as a palliative therapy modality.

Case Report

A 32-year-old female patient in whom weight gain of 20 kg had been noticed over 1 year was admitted. In addition, there had been signs of virilization, secondary amenorrhea and leg edema for a few months.

Primary diagnostics were carried out at her local hospital by means of abdominal sonography and computer tomography (CT) and showed a space occupation of 11.5×10 cm in the region of the right adrenal. In addition, bilobular multiple hepatic metastases of varying sizes could be demonstrated. A liver focus was biopsied for further clarification. Histological and immunohistochemical appraisal elsewhere revealed a clear cell carcinoma corresponding to a metastasis of an adrenocortical carcinoma.

For further diagnostics and treatment, the patient was transferred to our hospital. On physical examination, we found a very adipose patient with a reduced general condition. She was hypertensive with blood pressure values up to 160/105 mmHg and a heart rate at 80/min. In addition to the initial admission, as described above, a pressure-dolent abdomen with distinct guarding was very prominent. Besides, she reported on severe attacks of anxiety. At the same time, she was suffering from depression.

A current computer tomography showed a distinct progression in terms of size of the primary tumor and the liver metastases. By angiographic examination infiltration of the kidney could be ruled out. In addition, pulmonary and skeletal metastases could be excluded. There were pathological changes in the clinical test parameters: LDH (4263 U/l), potassium (2.8 mmol/l) and aldosterone (963 pg/dl, normal 30–160 pg/dl), cortisol (76.8 µg/dl, normal 15–25 µg/dl), androstendione (>10.0 ng/ml, normal 1.0–4.4 ng/ml) and DHEA-S (dehydroepiandrosterone sulfate; >10.0 µg/ml, normal 0.8–3.4 µg/ml). The synthetic liver activity was normal apart from lowered total protein (4.9 g/dl) and albumin (2.2 g/dl). In particular, ammonia and lactate were in the normal range.

Furthermore, the excretion of DHEA-S and the corresponding metabolites as well as THS (11-deoxy-tetrahydrocortisol) in the urine were excessively raised.

Clinical Course

The patient had an advanced hormonally active adrenocortical carcinoma (tumor stage T3 N1 M1, corresponding to clinical stage IV) with hepatic metastases. A local surgical procedure was not possible because of the tumor size and the pronounced hepatic metastases. Moreover, the general condition of the patient was greatly reduced. In view of the already poor liver function, we used ketoconazole to block steroid synthesis. The potassium level could be raised to the normal range by substitution and administration of an aldosterone antagonist.

Because of this palliative situation, a local treatment measure, namely regional embolization, was chosen primarily with the objective of rapid alleviation of pain and the abdominal tension. Therefore transvascular embolization, with a total of 11 ml ethibloc administration, was carried out in the same session with the diagnostic angiography. Following repeated computer tomographic checks did not show any criteria for inflammation or perforation.

After the embolization a pronounced alleviation of the pain and improvement of the general condition of the patient was significant. This clinical condition was stable for about 10 days. In this short phase, there was also an impressive brightening of the initially depressive mood.

Then renewed clinical and laboratory test values rapidly deteriorated. This correlated with an explosive increase in size of the nonembolized metastases in both liver lobes. Systemic chemotherapy was then started with 100 mg etoposide i.v. and 300 mg carboplatin i.v., but had to be discontinued because of a fulminant kidney failure, respiratory deterioration, and somnolence of the patient. The patient died of multiorgan failure with massive tumor progression and the clinical suspicion of sepsis.

At autopsy, a metastasized right adrenocortical carcinoma was found (weight 460 g, size 17×9×7 cm) with multiple liver metastases (up to 5 cm in diameter) and a high degree of hepatomegaly (weight 4650 g). Considering the embolization, a vessel branch of the cranial renal artery, leading to the cranial pole of the tumor was obliterated by embolization material up to the peripheral vascular bed. The cranial part of the tumor showed extensive necroses up to 8.5 cm in diameter (fig. 1). The right hepatic artery was also obliterated in its entire course up to the arteries of the portal fields (fig. 2). The right liver lobe showed a pronounced parenchymal necrosis (15 cm in diameter).

Discussion

The prognosis of the adrenocortical carcinoma is unfavorable and mainly depends on the tumor stage at the time of diagnosis [8, 9]. Only in early stages surgery can result in constant cure. The median survival time for stages III and IV is 0.6 years [10]. The disease is often diagnosed in advanced stage and for this therapy modalities frequently published report on individual experience or illustrate patient groups which are heterogeneous with regard to the tumor stages, so that no generally valid treatment protocols have been described [3, 2]. In case of inoperability, alternative treatment remains only palliative, e.g. chemotherapy, radiation or other local procedures. Intraarterial

Fig. 1: Autopsy finding: Preparation of the adrenocortical carcinoma.

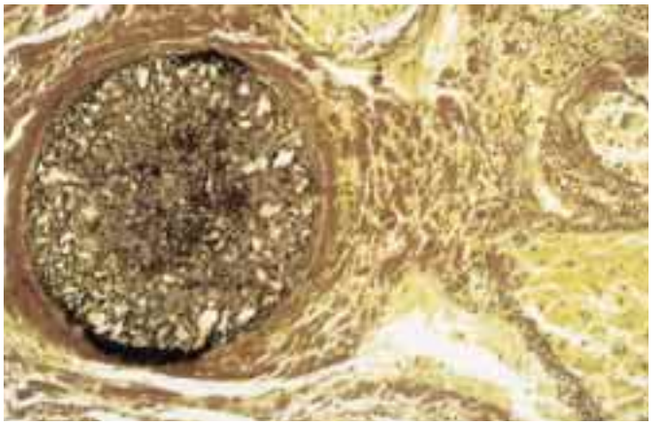

Fig. 2: Autopsy finding: Histology of a portal field, embolization material in the artery stained brown (eosin-von Gieson, magnification × 100).

embolization with lipidol or ethibloc, which causes ischemic necrosis of the tumor, has been used as palliative treatment either alone or in combination (chemoembolization). The combination, described often as therapy for hepatocellular carcinoma, is very toxic and did not significantly improve survival. Embolization is considered as very effective on the basis of reports of a rapid decrease in tumor size [11].

Therefore, in the reported case tumor embolization was chosen as first therapy, especially because a rapid clinical effect could be expected, although it was quite sure that it might not have a positive effect on survival, but might improve the quality of life. To avoid toxicity in a situation with diffuse hepatic metastasis the embolization was performed without the combination with chemotherapy. The latter should be performed as systemic modality in a second step. Because of the great overall extent of the tumor, radiation with a justifiable radiotherapeutic target volume was not practicable.

The indication and methodological procedure of tumor embolizations have been discussed in many reports [12, 5]. Kauffmann and Richter [5] make special reference to the selection and the methodological procedure in tumor embolization. Ethibloc, which consists of zein (a gelatinous maize protein), is appropriate when, like in this case, a homogeneous occlusion of the capillary vascular compartment, is intended. The mechanism of occlusion is based on precipitation of the gel in the blood and on controlling the embolization plane with alcohol and glucose, which were added to the solvent. A distinct peripheral to capillary occlusion type results without the danger of venous dissemination, which is shown in the histological preparation of the liver metastasis of the reported patient (fig. 2).

Systemic treatment is indicated in failure of local measures or tumors which are primarily inoperable or cannot be otherwise approached regionally, and in metastatic spreading. Most experience is available with mitotane (o,p'-DDD), especially in hormone-producing tumors. The substance has been developed from the insecticide DDT and is characterized by a high adrenolytic action. However, mitotane is considered to have many side effects and therefore often cannot be given in maximum doses [13].

Ketokonacol, aromatase inhibitors (e.g. aminogluthetimide) [2, 10] and suramin are available for isolated antihormonal purposes. These substances primarily alleviate the clinical symptoms resulting from hormone overproduction. Objective remissions, such as have been described for mitotane under a standard dosage (6–10 g/day) with 20–25% [14], are not expected.

Besides the substances specified, classical chemotherapy can also be employed in advanced metastasized adrenocortical carcinoma. Doxorubicin, BCNU, 5-fluorouracil and methotrexate appear to be effective single substances [2, 15]. An action on the tumor in adrenocortical carcinoma is also ascribed to cisplatin, especially in combination treatments. A remission rate of 23% could be attained under therapy with cisplatin, doxorubicin and 5-fluorouracil. These series included 1 patient with a complete remission persisting for 4 years [10]. After administration of cisplatin, etoposide and bleomycin, 2 out of 4 patients attained a remission [16]. An overall response rate of 53.5% could be achieved by combining mitotane with the cytotoxic drugs etoposid, doxorubicin, and cisplatin [17].

In a case report, Zidan et al. [18] reported on the response of a female patient with liver metastases after 5 cycles of chemotherapy with cisplatin and etoposide. The remission was maintained for 17 months; surgical resection of the liver metastases was carried out after the end of cytostatic therapy [18]. Other study groups also confirmed tumor regression under this combination of cytostatics [19]. By analogy, we chose the more recent derivative carboplatin as a less nephrotoxic substance. The combination of carboplatin with etoposide appeared appropriate, since positive experience is also available with other tumor diseases which are primarily refractive in individual cases such as small-cell lung cancer, germinal cell tumors, and neuroendocrine neoplasias [20, 21]. Because of the impressive clinical improvement after the embolization, there was made the decision for systemic chemotherapy at time of progression of the nonembolized liver metastasis.

The rapid further progression of the tumor with simultaneous clinical deterioration compelled us to discontinue chemotherapy before its completion, so in the case presented no appraisal can be made with regard to response to this treatment. It cannot be excluded that the chemotherapy played an additional role in the described organ failure. Our positive interim expe-

rience concerned the therapeutic use of embolization. We conclude that tumor embolization could be an effective method to improve the quality of life in patients with an isolated symptomatic inoperable tumor or with isolated metastasis. In the case discussed above this effect was limited early by the rapid progress of the diffuse liver metastasis.

References

1 Favia G, Lumachi F, Carraro P, D'Amico DF: Adrenocortical carcinoma. Our experience. Minerva Endocrinol 1995;20:95–99.

2 DeVita VT, Carbonne PP, Owens AH: Clinical trials with 1,3-bis (2-chloroethyl)-1-nitrosourea NSC-409962. Cancer Res 1965;25:1876–1881.

3 Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P: The Italian Registry for Adrenal Cortical Carcinoma: Analysis of a multiinstitutional series of 129 patients. Surgery 1996;119:161–170.

4 Lee JE, Berger DH, El-Naggar AK, Hickey RC, Vassilopoulou-Sellin R, Gagel RF, Burgess MA, Evans DB: Surgical managemant DNA content, and patient survival in adrenal cortical carcinoma. Surgery 1995;118:1090–1098.

5 Kauffmann GW, Richter GM: Embolisation der Niere; in Günther RW, Thelen M (eds): Interventionelle Radiologie. Stuttgart, Thieme, 1988, pp 171–185.

6 Regge D, Balma E, Lasciarrea P, Martina C, Serrallonga M, Gandini G: Interventional radiology of the adrenal glands. Minerva Endocrinol 1995;20: 15–26.

7 Castro de F, Isa W, Aguera L, Rosell CD, Abad JI, Robles JE, Zudaire JJ, Berian JM: Primary adrenal carcinoma. Actas Urol Esp 1993;17:30–34.

8 Lobo-Sanahuja F, Estrada-Molina Y, Gonzalez M, Calzada LD, Fuscaldo C, Artavia-Loria E, Garcia I: Functioning tumors of the adrenal cortex in children. Clinical and therapeutic considerations on 11 cases. Bol Med Hosp Infant Mex 1993;50:655–661.

9 Teinturier C, Brugieres L, Lemerle J, Chaussin JL, Bougneres PF: Adrenocortical carcinoma in children: retrospective study of 54 cases. Arch Pediatr 1996;3:235–240.

10 Schmoll HJ, Dralle H: Nebennierenrindenkarzinom; in Schmoll HJ, Höffken K, Possinger K: Kompendium Internistische Onkologie, Teil 2. Heidelberg, Springer, 1997, pp 895–913.

11 Groupe D'Etude et de Traitement du Carcinome Hepatocellulaire: A Comparison of Lipiodol Chemoembolization and conservative Treatment for unresectable Hepatocellular Carcinoma. N Engl J Med 1995;332:1256–1261.

12 Günther RW, Klose K, Thelen M, Jacobi G: Superselektive Embolisation mit Gewebekleber im Urogenitaltrakt. Fortschr Röntgenstr 1984;134:536–539.

13 Anderson A, Warren DJ, Nome O, Vesterhus L, Slordal L: A High-pressure liquid chromatographic method for measuring mitotane (11-(o,p'-dichlorodiphenyl)-2,2-dichloroethane) and its metabolite 1,1-(o,p'-dichlorodiphenyl)-2,2-dichloroethene in plasma. Ther Drug Monit 1995;17:526-531.

14 Luton JP, Cerdas S, Billaud L, Thomas G, Guilhaume B, Bertagana X, Laudat M-H, Louvel A, Chapuis Y, Blondeaus P, Bonnin A, Bricaire H: Clinical features of adrenocortical carcinoma, prognostic factors and the effect of mitotane therapy. N Engl J Med 1990; 322:1195–1201.

15 Friedman MA, Ignoffo RJ, Resser KJ: Combination 5FU and moderate dose methotrexate (MTX) and Leukovorin (L) – Phase I-II study of patients with disseminated colorectal cancer. Proc Am Assoc Cancer Res/Am Soc Clin Oncol 1979;20:(abstr).

16 Hesketh PJ: Chemotherapy of adrenocortical carcinoma. Proc Am Soc Clin Oncol 1986;5:561.

17 Berruti A, Terzolo M, Pia A, Angeli A, Dogliotti L: Mitotane associated with etoposide, doxorubicin, and cisplatin in the treatment of advanced adrenocortical carcinoma. Italian Group for the study of Adrenal Cancer. Cancer 1998;83:2194–2200.

18 Zidan J, Shpendler M, Robinson E: Treatment of metastatic adrenal cortical carcinoma with etoposide (VP-16) and cisplatin after failure with o,p'DDD. Clinical case reports. Am J Clin Oncol 1996;19:229–231.

19 Norton JA: Adrenal tumors; in DeVita VT, Hellmann S, Rosenberg StA (eds): Principles and Practice of Oncology, section 4, ed. 4. Philadelphia, PA, Lippincott-Raven, 1997; pp 1659–1677.

20 Hainsworth JD, Williams SD, Einhorn LH, Birch R, Greco FA: Successful treatment of resistant germinal neoplasms with VP-16 and cisplatin: Results of a Southeastern Cancer Study Group trial. J Clin Oncol 3, 1985,666–671.

21 Porter LL, Johnson DH, Hainsworth JD, Hande KR, Greco FA: Cisplatin and etoposid combination chemotherapy for refractory small cell carcinoma of the lung. Cancer Treat Rep 1985;69:479–481.