Abstract. Background: Adrenocortical carcinoma (ACC) is a rare tumour, sometimes causing glucocorticoid hypersecretion. Treatment guidelines have not been established, but are currently under investigation. Case Report: A 55-year-old Caucasian woman presented with adrenal Cushing’s disease. Histological examination after a left adrenalectomy revealed a benign tumour. Postoperatively, elevated serum cortisol levels normalized. Hypercortisolism occurred again two years later. Diagnostic work-up revealed hepatic metastatic lesions of an ACC which were treated by right hemihepatectomy. Initial histological diagnosis was revised according to the increased proliferative changes. Postoperatively, cortisol declined to normal levels. Treatment with mitotane (o, p'-DDD) as a cytostatic agent was not tolerated. One year later, the patient was diagnosed with a solitary osseous metastasis at the left side of the sacrum because of back pain. Following curettage and stabilization, radiotherapy of this region with 37.5 Gy was performed, improving slightly elevated cortisol levels and neurological symptoms. Conclusion: Careful clinical and radiographic follow-up of patients with ACC are important. In this case of oligometastasizing ACC, serum cortisol values correlated with the metastatic potential of the tumour indicating that small elevations of cortisol should initiate the search for a potential progression of the tumour.

Materials and Methods

Serum cortisol levels were determined at the laboratory of the Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, using a commercial immunoassay kit (ADVIA CENTAUR® CP, Immunoassay system with direct chemiluminescence technology, Bayer Health Care Diagnostics, Fernwald, Germany). The lower reference value of this immunoassay for serum cortisol is at 5 ìg/dl, the top reference value is at 25 ìg/dl. Follow-up was regularly carried out at three-month intervals. The follow-up procedure included disease-specific history, physical examination, abdominal ultrasound, and laboratory tests, including measurement of serum and urinary cortisol levels. In case of suspected relapse, specific diagnostic procedures, such as bone scintigraphy, were performed.

Case Report

We report the case of a 55-year-old Caucasian female patient with a metastatic endocrine-active adrenocortical carcinoma (ACC) (Table I). Initially, the patient presented with Cushing’s syndrome of unknown origin. After revealing a 6 cm adrenocortical tumour on the left side by computer tomography of the abdomen, an adrenalectomy was performed. Histological examination did not demonstrate distinct malignant behaviour so that an atypical adrenal adenoma was suspected of causing the Cushing’s syndrome.
at that time. Postoperatively, serum cortisol levels declined to reference values (Figure 1). Two years later, hypercortisolism recurred, again causing Cushing’s disease. Diagnostic imaging showed unclear hepatic lesions. Assuming metastases of a malignant tumour, a modified right hemihepatectomy for complete resection was performed. Histopathological examination confirmed metastases of an ACC; subsequently the prior diagnosis of an atypical adrenal adenoma was corrected. Postoperatively, serum cortisol levels declined to reference values again (Figure 1). Because of the metastatic disease, an additional application of \( \text{o}, \text{p}'-\text{DDD} \) (mitotane) was begun, but not tolerated by the patient. One year after hemi-hepatectomy, an osseous metastasis occurred at the left side of the sacrum causing severe pain and neurological symptoms, particularly a sacral radiculopathy, and a concurrent relapse of hypercortisolism caused Cushing’s disease again. Diagnostic imaging by CT, MRI, scintigraphy and PET showed a solitary lesion. Curettage and stabilization was followed by radiotherapy of this region with 37.5 Gy (daily dose: 2.5 Gy; 5 x/week), reducing cortisol levels to reference values (Figure 1). After multimodal treatment, pain and neurological symptoms improved.

### Discussion

The clinical presentation of adrenocortical carcinoma (ACC) can be similar to the clinical picture of adrenal adenoma. Abdominal ultrasound, computed tomography and magnetic resonance imaging have improved the capability to diagnose and to determine the progress of ACC, but often fail to differentiate between benign and malignant tumours. Therefore, histological demonstration of invasion of the capsule and blood vessels by tumour cells is mandatory for the diagnosis of ACC, particularly in cases without secondary signs of malignancies, e.g. without invasion of tumour into surrounding tissue, lymphadenopathy, or distant metastases (4). Due to problems with the histological classification of adrenal tumours (5), the diagnosis of ACC may remain difficult so that sometimes the initial diagnosis of an atypical adrenal adenoma must be revised to that of ACC, at the latest when metastases occur, as seen in the presented case.

Although complete resection of ACC is the only effective therapy, a relapse can be observed in 23% to 80% of cases, within a mean disease-free interval of 12-22 months. Additionally, between 30% and 50% of patients already show metastatic disease at the time of diagnosis, leading to a stage-independent 5-year overall survival of 19% to 38%. For patients with an initial UICC stage I/II, as in our case, a 5-year overall survival of 43% to 78% is reported in the literature (6, 7).

Distant metastases affect most often liver (46%) and lungs (46%), followed by lymph nodes (40%), peritoneum (40%) and bone (17%) (8). The prognosis of patients with refractory or metastatic ACC is said to be very poor, although a few reports have indicated that aggressive multimodal treatment, including complete resection of local recurrences or of singular distant metastases of ACC, could lead to an improved survival rate in patients with such advanced forms of ACC (2, 7, 9).

Treatment options of metastatic disease of ACC are limited because chemotherapy and radiotherapy generally do not provide any significant improvement in overall survival. In contrast, palliative radiotherapy for metastatic disease is effective in a significant percentage of patients
and is the treatment of choice for bone metastases. Additionally, radiotherapy may be important for the postoperative treatment of patients with a high risk of local recurrence (3). For the treatment of bone metastases in the presented case, additive radiotherapy was delivered postoperatively because radical surgery of the sacrum had been avoided due to the fear of surgery-related morbidity. The pharmacological drug α, p'-DDD (mitotane), an isomer of the insecticide p,p'-DDD and a chemical congener of the insecticide DDT, is the only adrenal-specific medical agent available for the treatment of ACC. Mitotane is effective against ACC in approximately 25% of cases, leading to objective tumour regression, and is able to control and prevent hormone excesses in the majority of patients. Nevertheless, side-effects occur frequently during mitotane treatment, affecting mainly the gastrointestinal tract and central nervous system. Since not all patients respond to mitotane therapy, it is one of the challenges for the future to define the subset of patients who will respond to mitotane, so that unnecessary side-effects will be avoided in patients who are unlikely to respond to this toxic drug (10).

The correlation between the clinical status of the patient and alterations in tumour size, determined by different imaging methods, has been the most important and most frequently used method for evaluation of treatment success. However, in certain cases the therapeutic effect could also be assessed by marker substances characterizing biological activity of the tumour. Tumour markers are already used in clinical practice to assess the status of malignant tumours after surgery as well as after other tumour-specific therapies (11-13). Preoperative and postoperative levels of these tumour markers are essential for an appropriate evaluation of the course of the tumour.

In most cases, changes of serum levels of tumour markers correlate with the therapeutic effect: the lower the level of the tumour marker after therapy, the stronger the impact of this therapy on tumour proliferation. Thus, it is valid to estimate the success of any treatment on tumour proliferation by measuring tumour markers (14). Referring to ACC, approximately 60% of adult patients show cortisol hypersecretion, being the most common hormone excess of this tumour burden. Adrenal Cushing’s syndrome is the most frequent clinical presentation in functional ACC, as seen in our case. In patients without clinical symptoms, subtle endocrine dysfunctions are often detected by a thorough laboratory work-up (15). Unfortunately, the pattern of hormone secretion may vary in functional ACC and multiple combinations of hormone excesses are encountered. Additionally, several investigators reported that endocrine activity can vary in the course of ACC, e.g. primarily endocrine-active tumours may change into inactive tumours and vice versa (1, 8). Endocrine profiles of functional ACC show only little influence on management of therapy and follow-up, in particular, of recurrent or metastasized ACC. Nevertheless, for individual patients with endocrine-active ACC, serum cortisol levels or levels of other endocrine markers, e.g. dehydroepiandrosterone sulphate (DHEAS), may serve as tumour markers during follow-up, as in our case. However, lab results of patients after treatment showing increased endocrine marker levels at the top reference value can be difficult to interpret. Our presented data emphasize the necessity of interpreting serum courses of tumour markers only in correlation with clinical and imaging data as well as other laboratory tests in order to avoid misinterpretations, as has been reported by other investigators (16).

Conclusion

This case report emphasizes the need for careful clinical and radiographic follow-up of patients with recurrent or metastasized ACC. In our presented case of functional ACC, serum cortisol levels correlated with the clinical course of the patient. A surgical approach with consolidating radiotherapy should be adopted to provide symptom control and possible long-term survival in oligometastatic disease.

References


