Hormonal treatment of metastatic prostate cancer is a well-established therapy. Although in past decades surgical options such as orchidectomy, adrenalectomy, or hypophysectomy predominated, medical treatments with antiandrogens and GnRH analogs have now become the gold standard, and most surgical procedures are now only rarely used in the treatment of widespread prostate cancer. However, despite developments in hormone therapies as well as cytotoxic chemotherapies, the prognosis of metastatic prostate cancer remains poor and there is a need for additional treatment options, which may revive some of the older concepts. Here, we present the case of a patient with metastatic prostate cancer who we treated with hypophysectomy. This case may provide further ideas for palliative treatment, including dopamine agonist or somatostatin analog therapy in patients with progressive prostate cancer.

Case Report

History and Presentation. This 63-year-old man suffering from metastasized prostate cancer presented to us with rapidly developing bilateral cavernous sinus syndrome. He was being treated with palliative GnRH ana-
log therapy (leuprorelin) and chemotherapy (docetaxel) as well as long-term prednisone therapy (7.5 mg/day), but complained of severe bone pain despite significant analgesic treatment.

Examination. On examination we observed that the patient was adynamic and appeared anemic. He had an elevated temperature (38.5°C), signs of sinusitis, bilateral incomplete ophthalmoplegia, and no significant decrease of visual fields. No other neurological deficits were present. The patient underwent an emergency MR imaging study (Fig. 1).

Laboratory studies confirmed the clinical impression of anemia (hemoglobin 8.6 g/dl, leukocytes $3.2 \times 10^9$/L, thrombocytes $92 \times 10^9$/L), and an elevated C-reactive protein level (150 mg/L). Endocrinological parameters on admission are shown in Table 1.

Treatment Considerations. The patient was initially treated with antibiotics and erythrocyte transfusion. After an unsuccessful trial of high-dose dexamethasone therapy, we discussed the treatment options with the patient and his oncologist. Radiotherapy was not considered likely to be beneficial due to the already significant compression of the optic nerves and fear of further swelling. We therefore recommended a selective transsphenoidal removal of the pituitary tumor to indirectly decompress the nerves within the cavernous sinus. Furthermore, the additional resection of the anterior lobe of the pituitary gland was discussed as a palliative hormonal treatment for the prostate cancer, especially with respect to the patient’s bone pain.

We decided upon this latter option because of the additional palliative potential, particularly as the patient showed high-normal IGF-I and prolactin levels.

Operation. Written consent was obtained and the patient underwent ultra direct microscopic transnasal–transsphenoidal surgery through the right nostril in a semisitting position. Inflamed mucosa within the sphenoid sinus was removed, the floor of the sella was drilled with a diamond drill, and the carotid arteries were located within the cavernous sinus by means of a microDoppler device as previously described.10,18 The tumor was removed (by J.F.) and diagnosed as a regular pituitary adenoma by cytology and frozen sections. Afterward, a hypophysectomy with preservation of the posterior lobe as well as the stalk was performed (by D.K.L.) with visualization of both rims of the cavernous sinus, showing tumor tissue growing out of the cavernous sinus area. After appropriate hemostasis was achieved the sella was filled with muscle from the lateral portion of the rectus femoris muscle. Postoperative MR imaging verified the improvement of the intrasellar alterations (Fig. 2).

Histological Findings. Histological investigation of the specimen revealed a highly vascularized epithelial tumor composed of polygonal, densely packed, mildly pleomorphic cells with round nuclei and prominent nucleoli and growing as a solid mass (Fig. 3). The tumor cells were immunoreactive for FSH and LH (Fig. 4a and b), showed only low proliferative activity as determined by Ki 67 immunostaining (Fig. 4c) and did not stain for cytokeratin (Fig. 4d). The tumor was diagnosed as a clinically non-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop</th>
<th>Postop</th>
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<tr>
<td>prolactin (μg/L)</td>
<td>21.4</td>
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</tr>
<tr>
<td>LH (U/L)</td>
<td>&lt;1.7</td>
<td>&lt;1.7</td>
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<tr>
<td>FSH (U/L)</td>
<td>&lt;1.5</td>
<td>&lt;1.5</td>
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<tr>
<td>TSH (mU/L)</td>
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<td>&lt;0.02</td>
</tr>
<tr>
<td>ACTH (ng/L)</td>
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<td>&lt;10</td>
</tr>
<tr>
<td>hGH (mU/L)</td>
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<td>&lt;1</td>
</tr>
<tr>
<td>IGF-I (μg/L)</td>
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<td>31.3</td>
</tr>
<tr>
<td>testosterone (μg/L)</td>
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<td>&lt;0.05</td>
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<tr>
<td>free T4 (pmol/L)</td>
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<td>4.3</td>
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<tr>
<td>PSA (μg/L)</td>
<td>1216</td>
<td>876</td>
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</table>

* Values for cortisol are not reported because the patient was receiving long-term treatment with 7.5 mg prednisone daily. Abbreviations: ACTH = adrenocorticotropic hormone; hGH = human growth hormone; TSH = thyroid-stimulating hormone.
secreting pituitary adenoma immune-reactive for LH and FSH. Within the adenoma, small, circumscribed nests of large pleomorphic cells with prominent nuclear polymorphism and conspicuous mitotic activity were identified (Fig. 3). Approximately 80% of these tumor cells were labeled with Ki 67 antibodies (Fig. 4c). The pleomorphic tumor cells showed weak immunoreactivity to antibodies against PSA (Fig. 4e) and stained strongly positive for cytokeratin (Fig. 4d). Interestingly, most of these tumor cells were located within blood vessels, as determined by immunostaining for CD 34 (Fig. 4f). Thus, the specimen comprised 2 different tumor entities, leading to the diagnosis of a metastasis of an adenocarcinoma of the prostate within a clinically nonsecreting pituitary adenoma.

Postoperative Course. After the surgery the patient recovered rapidly from the cavernous sinus syndrome. Additionally, the severe generalized bone pain nearly re-

Fig. 3. Photomicrograph demonstrating a pituitary adenoma with islets of carcinoma cells within the lesion (arrows). H & E, bar = 50 μm.

Fig. 4. Photomicrographs demonstrating the immunohistochemical characterization of the specimen. The adenoma cells show expression of FSH (a) and LH (b) and low proliferative activity (c) while the metastatic carcinoma cells show expression of cytokeratins (visualized with AE1/AE3 antibodies [d] and a high proliferative activity (c). Single carcinoma cells show weak expression of PSA (e). Note the mainly intravascular localization of carcinoma cells shown in the staining for endothelial cells (CD 34, f).
Hypophysectomy for prostate cancer

solved, allowing a dramatic reduction of analgesia. The postoperative endocrinological parameters are shown in Table 1. Prednisone therapy (7.5 mg/day) was continued, the patient was started on a low-dose levothyroxine therapy (50 μg/day). No testosterone- or hGH substitution therapy was considered. The posterior lobe function was preserved without signs of diabetes insipidus. The patient was discharged 10 days after surgery in improved physical condition and nearly pain free.

Because of ongoing disease, the ambulatory docetaxel chemotherapy was continued. However, the patient’s health deteriorated further, resulting in readmission to the hospital because of anemia and septicemia. Despite antibiotic treatment the patient died 4 months after the transsphenoidal surgery. During the 4 months no further pain therapy was needed, and the patient remained nearly pain free.

Discussion

In 1972, Huggins and Hodges12 first reported on the effects of castration on metastatic prostate cancer. In the following decades, castration by orchidectomy leading to androgen withdrawal became a standard treatment in prostate cancer. Other options of hormone treatment, such as estrogen therapy, were discovered and further developed. In 1948, Scott performed the first hypophysectomy in a patient with prostate cancer. The patient died, probably due to hypocortisolism (cortisone became available 1950).30 In 1952, Luft et al.19 became the first authors to report a successful hypophysectomy, Scott and Schirmer30 published a report on a series of 17 patients undergoing hypophysectomy for prostate cancer. They concluded that patients who had ongoing disease (despite previously successful hormone treatment such as castration or estrogen therapy) and residual androgen production might benefit the most from hypophysectomy. In the following years, further studies were published with objective “remission” rates of 35–53%. An average survival time of 15.8 months (range 6–28 months, 34 patients) was reported, compared with 4 months in patients who had not undergone hypophysectomy.23 Another therapeutical aspect of hypophysectomy in the treatment of prostate cancer is its effect on metastatic bone pain. In general, a success rate of up to 80% was reported for otherwise therapy-resistant bone pain in patients with metastatic disease.5,20,31 According to a current theory, androgen-independent tumor progression especially in bone metastases can be explained by a release of “survival factors” within the microenvironment of the metastasis-surrounding bone tissue, protecting the carcinoma cells from androgen ablation.13 Frequently, the metastases grow, while the primary tumor site is stable.14,28

In the decades following the introduction of GnRH analogs, surgical treatments such as adrenalectomy and hypophysectomy became nearly obsolete.

Unfortunately, prostate cancer cells only respond to androgen withdrawal for a limited time; the tumors eventually become androgen-independent.20,23 Other pituitary hormones, including prolactin, growth hormone, IGF-I, and possibly LH, are known to play an important role in prostate tissue.26 Prolactin, for example, is important for proliferation as well as for differentiation of prostate tis-

References

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