Malignant prolactinoma: case report and review of the literature

Marleen Kars, Ferdinand Roelfsema, Johannes A Romijn and Alberto M Pereira

Department of Endocrinology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands

(Correspondence should be addressed to M Kars; Email: m.kars@lumc.nl)

Abstract

Pituitary carcinomas are extremely rare. In general, the initial clinical, biochemical, and histological characteristics are of minimal utility in distinguishing benign adenomas from pituitary carcinomas. We describe a 63-year-old woman with a macroprolactinoma, who presented with diplopia and blurred vision. This unusual initial presentation and the subsequent aggressive clinical course, with diffuse local and distant intramedulary metastases, prompted us in retrospect to make a detailed analysis of the therapeutic interventions and histology. In addition, we reviewed all available literature on published cases of malignant prolactinoma and detailed their epidemiological, clinical, and histopathological characteristics. In brief, it is postulated that pituitary carcinomas arise from the transformation of initially large, but benign, adenomas. Unusual and/or atypical clinical manifestations appear to occur more frequently. In vivo, the development of dopamine agonist resistance in invasive macroprolactinoma is indicative of malignancy and should prompt the clinician to perform a biopsy of the tumor. For pituitary tumors that exhibit high mitotic activity, increased Ki-67 and/or p53 immunoreactivity, it may be useful to denote these tumors as 'atypical' prolactinomas to raise the possibility of future malignant development.

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Introduction

Although pituitary tumors are relatively common, occurring in approximately 10–20% of normal subjects on autopsy or magnetic resonance imaging (MRI), the incidence of pituitary carcinoma is extremely low (1). To date, a total of approximately 140 cases have been reported, one third of them being malignant prolactinomas (2). The histological, clinical, and biochemical characteristics are reported to be of minimal utility in distinguishing benign from malignant tumors, unless (distant) metastases have developed. Presently, it is postulated that pituitary carcinomas arise from the transformation of initially large but benign adenomas (1). The arguments are based on observations that the initial presentation is not different from other macroadenomas, the long-duration needed for the transformation into carcinoma, and the increasing accumulation of genetic aberrations (3). We describe a patient with a malignant prolactinoma, whose unusual initial presentation and clinical course prompted us, in retrospect, to make a detailed analysis of the case with respect to the therapeutic interventions and histology. For comparison, we reviewed all published cases of malignant prolactinoma and detailed their epidemiological, clinical, biochemical, and histological characteristics.

Case report

A 63-year-old woman, who presented with diplopia and blurred vision, was diagnosed with a macroprolactinoma in 1998. On neurological examination, ptosis of the right eye was present, together with abducens palsy and impaired convergence. Furthermore, bitemporal hemianopsia was present (Fig. 1). Prolactin concentration was increased 20-fold: 490 µg/l (normal value <22 µg/l). MRI showed a pituitary mass with a diameter of 2.5 cm, extending into the right sphenoidal sinus as well as the cavernous sinus and compressing the temporal lobe (Fig. 2). Therapy was initiated with bromocriptine (1.25 mg t.i.d) resulting in normalization of the visual fields and decrease in prolactin levels to 56 µg/l within a few months.

The visual field defects recurred and prolactin levels increased to 206 µg/l (Fig. 3), 6 months later. Therefore, bromocriptine treatment was switched to quinagolide (up to 300 µg/day). Nonetheless, in January 2000, MRI showed progression of the pituitary tumor with encasement of the internal carotid artery and compression of the optic chiasm. The macroprolactinoma did not react satisfactory to medical treatment, even with cabergoline, which was stopped, since prolactin levels progressively increased in the presence of further progression of tumor.
growth. Furthermore, she developed progressive anterior pituitary insufficiency (de novo adrenocorticotropin hormone and thyroid-stimulating hormone deficiency) and the visual field defects increased. Therefore, she was operated in April 2000. Decompression of the optic chiasm was performed via transcranial route. Histological investigation of the tumor revealed positive immunostaining for prolactin without mitotic activity, but high Ki-67 (MIB-1) labeling index (10–15%). Fractionated conventional radiotherapy was administered by a linear accelerator (6 MeV) in a total dose of 54 Gray (Gy) in June 2000. Thereafter, prolactin concentrations decreased gradually without dopaminergic therapy from 445 µg/l in June 2000 to a nadir of 33 µg/l in February 2001 (Fig. 3). The effect on tumor volume in response of radiotherapy was evaluated 8 months after radiotherapy with MRI. A slight reduction in tumor volume was noted. Encasement of the internal carotid artery persisted.

Serum prolactin levels started to rise again in August 2001. MRI of the brain did not reveal progression of the tumor, but the rise in prolactin concentration proved to be due to metastases in the spinal cord (Fig. 4), which was confirmed with epidepride (dopamine D2 receptor) scintigraphy (Fig. 5). Laminectomy was performed in December 2001 because of compression of the myelum in the sacral region, followed by fractionated radiotherapy (6 × 4 Gy) from L5 to S5 in February 2002. Histological examination confirmed a prolactin-producing metastasis.

Subsequently, the patient developed extensive metastases throughout the spinal cord. Therefore, the spinal cord was irradiated with fractionated radiotherapy aimed at C2 to L4 with a total dose of 40 Gy in June 2002 to relieve pain and prevent paralysis from compression of the myelum.

In August 2002, she developed progressive ptosis of the right eye and facial paralysis due to infiltration of the tumor into the orbital cavity. Repeat radiotherapy to the skull (total dose of 25 Gy) was given in September 2002, resulting only in partial improvement of visual disturbances. However, prolactin concentrations continued to increase (Fig. 3) to a final concentration of 6000 µg/l in May 2003, 1 month before she died at home. Autopsy was not performed.

**Discussion**

Pituitary carcinomas are considered to arise from the transformation of initially large, but benign, adenomas (1). This notion is based on observations that

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**Figure 1** Visual field investigation in October 1999, revealing bitemporal hemianopsia.

**Figure 2** Magnetic resonance image (axial T1-weighted image) obtained in April 1999, demonstrating a pituitary mass of 2.5 cm, invading the right sphenoidal and cavernous sinus (Hardy classification IV-E (47)), and encasement of internal carotid artery.
demonstrate that the initial presentation of pituitary carcinomas does not differ from other (invasive) macroadenomas, the long-duration needed for transformation into a carcinoma, and the progressive accumulation of genetic aberrations (3). The present case of malignant prolactinoma is consistent with many, but not all, of these observations. This gave us an opportunity to compare carefully the data of our patient and review the intriguing features associated with malignant transformation of pituitary prolactinomas.

To date, only 47 cases of malignant prolactinoma have been reported, summarized in Table 1 (4–41). The first report of a patient with malignant prolactinoma was in 1981 by Martin et al. (4). Of the reported cases, 65% were male and the mean age at presentation was 44 years with a range of 14–70 years (Table 2). The presenting symptoms were related to hyperprolactinemia in 35% of the reported cases, including amenorrhea, galactorrhea, impotency, and decreased libido. At presentation, 71% of the patients had symptoms of local compression, such as headache and bitemporal hemianopia. Only five other patients presented with ptosis (27, 40), diplopia (34), oculomotor paresis (17), or lateral rectus paresis (13). Diabetes insipidus was a feature in only one patient (12). The treatment modalities after diagnosis were transsphenoidal or transcranial surgery (96%), radiotherapy (79%), chemotherapy (2%), and dopamine agonists (DA) in 65% of the cases (Table 3). A study by Isobe et al. shows that, in particular, large prolactinomas are very difficult to control with radiation doses between 50 and 60 Gy (42). Therefore, even benign prolactinomas do not respond very well to radiotherapy. The effect of radiotherapy on malignant prolactinoma has not been systematically documented. Therefore, a small response to radiotherapy, as in our case, cannot be interpreted as an indication of the malignant nature of the tumor.

The presentation of our patient with diplopia and blurred vision is a very unusual manifestation of pituitary macroadenoma. Such a presentation is most frequently associated with pituitary apoplexia. In the
absence of apoplexia, nerve paralysis is strongly suggest of compression or infiltration of the nerve, secondary to the high proliferative activity of the tumor. The presentation with diplopia as a result of oculomotor nerve paralysis has been reported previously in only one other case(17). In the present case, oculomotor nerve paralysis was due to tumoral orbital invasion (Fig. 2). Orbital invasion of a pituitary adenoma is very uncommon, being reported in only 16 patients, only 2 of whom manifested diplopia (43). Thus, in retrospect, the initial clinical and radiological presentation was highly indicative for an adenoma with high infiltrative potency.

Kaltsas et al. described histological and immunohistochemical parameters that predict the biological behavior of pituitary tumors (1, 3). Histological parameters associated with an atypical or aggressive behavior of the adenoma are cellular atypia, nuclear pleomorphism, more than two mitotic figures per ten high-powered fields, a proliferative index of Ki-67 more than 3%, positive p53 immunoreactivity, and invasion. They are also called atypical parameters. Histological investigation of the tissue initially obtained by surgery, biopsy, or autopsy of the prolactinoma revealed a benign classification in 37% and an atypical classification in 40% (Table 3). In the remaining 23% of cases, no documentation of the histological findings was given. The histological investigation in our case demonstrated a prolactinoma with a high proliferative index, such as nuclear pleomorphism and high Ki-67 labeling index. Estimation of the cell cycle-specific antigen Ki-67, using the MIB-1 antibody, has been demonstrated to correlate best with invasiveness and probably prognosis (1). Malignant and invasive tumors exhibit much higher Ki-67 labeling indices than benign adenomas (11.9 vs 4.66 vs 1.37% respectively) (44), although there is considerable case-to-case variability (1). Others even suggested that an increased Ki-67 labeling index is associated with secondary resistance or escape to DA treatment (45).

The time interval between the onset of symptoms at presentation and subsequent metastases in the

Figure 5 Total-body scintigraphy after $^{[123I]}$ epidepride injection in December 2001. Physiological accumulation of activity in basal ganglia, liver, kidneys, bowel, and urinary bladder. Anterior view (left image): intracranial accumulation of the isotope reflecting the macroprolactinoma (arrow). Posterior view (right image): multiple accumulations of the isotope reflecting multiple metastases in the spine (arrows).
<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Age/sex</th>
<th>Primary treatment</th>
<th>PA primary tumor</th>
<th>Time interval diagnosis – metastases (years)</th>
<th>Metastatic sites</th>
<th>Treatment of metastases</th>
<th>PA metastases</th>
<th>Cause of death</th>
<th>Time interval diagnosis – death (years)</th>
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</thead>
<tbody>
<tr>
<td>Martin, 1981</td>
<td>31/F</td>
<td>TSS, Rt, CT, DA, Rt</td>
<td>Pleomorphism, rare mitotic figures</td>
<td>5.5</td>
<td>Cerebellum</td>
<td>CT</td>
<td>Numerous mitotic figures</td>
<td>Death due to disease progression</td>
<td>8.5</td>
</tr>
<tr>
<td>Cohen, 1983</td>
<td>70/M</td>
<td>–</td>
<td>No mitotic figures(^b)</td>
<td>3.5</td>
<td>Cerebellopontine angle</td>
<td>–</td>
<td>No mitotic figures(^b)</td>
<td>Pulmonary edema, circulatory shock</td>
<td>3.58</td>
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<tr>
<td>U, 1984</td>
<td>63/M</td>
<td>CT, Rt</td>
<td>Mitosis 3/20 HPF</td>
<td>6</td>
<td>Cerebrum</td>
<td>CT, Rt, DA</td>
<td>Mitosis 11/20 HPF, pleomorphic Mitosis; tumor cells in subarachnoidal space and in venous blood channels</td>
<td>Pulmonary embolus</td>
<td>6.25</td>
</tr>
<tr>
<td>Gasser, 1985</td>
<td>28/M</td>
<td>CT, Rt, DA</td>
<td>Mitosis, pleomorphism</td>
<td>9</td>
<td>Cerebrum</td>
<td>CT, DA, Rt, CT</td>
<td>Mitosis, pleomorphism; tumor cells in subarachnoidal space and in venous blood channels</td>
<td>Death due to disease progression</td>
<td>12</td>
</tr>
<tr>
<td>Landgraf, 1985</td>
<td>44/F</td>
<td>CT, Rt, DA</td>
<td>Benign</td>
<td>4</td>
<td>Cerebellum, spinal cord</td>
<td>LT, Rt, DA, chemo, octapeptide-somatostatin, chemo</td>
<td>Benign</td>
<td>Death due to disease progression</td>
<td>5.5</td>
</tr>
<tr>
<td>Plangger, 1985</td>
<td>28/M</td>
<td>CT, Rt</td>
<td>Benign</td>
<td>9</td>
<td>Cerebrum, subarachnoid nodules</td>
<td>Cerebrum, vertebral bone, ribs</td>
<td>Mitotic figure rare</td>
<td>Still alive at publication</td>
<td>13.5</td>
</tr>
<tr>
<td>Scheithauer, 1985</td>
<td>52/F</td>
<td>Rt, CT, TSS(2x), DA</td>
<td>Mitotic figures rare</td>
<td>11</td>
<td>Cerebrum</td>
<td>CT, DA, CT, DA, Rt(2x)</td>
<td>Mitotic figure rare(^c)</td>
<td>Death due to disease progression</td>
<td>13.5</td>
</tr>
<tr>
<td>Von Werder, 1985 Muhr, 1988</td>
<td>43/F</td>
<td>CT, Rt, DA</td>
<td>Not documented Benign</td>
<td>4</td>
<td>Spinal cord</td>
<td>DA, LT, RT, DA Surgery, DA</td>
<td>Not documented Mitosis</td>
<td>Unknown</td>
<td>Still alive at publication</td>
</tr>
<tr>
<td>Atienza, 1991</td>
<td>34/M</td>
<td>DA, CT(2x), Rt, DA</td>
<td>No mitotic figures</td>
<td>4</td>
<td>Spinal cord</td>
<td>DA, Rt, TSS</td>
<td>Mitosis 2/10 HPF, vascular invas</td>
<td>Gastrointestinal bleeding</td>
<td>2.02</td>
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<tr>
<td>Popovic, 1991</td>
<td>47/M</td>
<td>DA, CT(2x), Rt</td>
<td>Mitosis 6/HPF</td>
<td>2</td>
<td>Dura, cerebrum, cerebellum</td>
<td>CT</td>
<td>Mitosis 6/HPF</td>
<td>Acute pulmonary edema, Staphylococcus aureus septicemia</td>
<td>12.33</td>
</tr>
<tr>
<td></td>
<td>56/F</td>
<td>TSS, Rt</td>
<td>Mitosis 5/10 HPF</td>
<td>12</td>
<td>Roof fourth ventricle, cerebrum, spinal cord</td>
<td>CT</td>
<td>Mitosis 5/10 HPF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) PA primary tumor: non-secretory adenoma
\(^{\text{b}}\) PA metastases: no mitotic figures
\(^{\text{c}}\) PA metastases: rare mitotic figures

Table 1 List of previously published cases of malignant prolactinoma.
<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Age/sex</th>
<th>Primary treatment</th>
<th>PA primary tumor</th>
<th>Time interval diagnosis – metastases (years)</th>
<th>Metastatic sites</th>
<th>Treatment of metastases</th>
<th>PA metastases</th>
<th>Cause of death</th>
<th>Time interval diagnosis – death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berezin, 1992</td>
<td>32/F</td>
<td>CT, Rt</td>
<td>Benign</td>
<td>20</td>
<td>Intraorbital</td>
<td>CT, enucleation left eye and retro-orbital mass, Rt</td>
<td>Mitosis 3–4/10 HPF, pleomorphism</td>
<td>Anorexia, pneumonia, comatose, death due to disease progression</td>
<td>25</td>
</tr>
<tr>
<td>Figarella, 1992</td>
<td>45/M</td>
<td>TSS, DA, CT(2x)</td>
<td>Mitosis 1/2 HPF</td>
<td>8</td>
<td>Vertebral, lung</td>
<td>–</td>
<td>Not documented</td>
<td>Unknown</td>
<td>Death due to disease progression</td>
</tr>
<tr>
<td>Kamphorst, 1992</td>
<td>45/M</td>
<td>CT, Rt, chemo, Rt</td>
<td>Mitotic figures rare</td>
<td>13</td>
<td>Pons, medulla oblongata, spinal cord</td>
<td>–</td>
<td>–</td>
<td>Unknown</td>
<td>Death due to disease progression</td>
</tr>
<tr>
<td>Petterson, 1992</td>
<td>40/M</td>
<td>CT, Rt, DA</td>
<td>Mitotic figures</td>
<td>5</td>
<td>Encasement carotid bifurcation, retro-orbital space, cerebrum, cerebellopontine angle, nodule vertebral artery</td>
<td>CT, DA, CT, chemo, CT, chemo</td>
<td>Pleomorphic, invading overlying cerebral tissue</td>
<td>–</td>
<td>Death due to disease progression</td>
</tr>
<tr>
<td>Assies, 1993</td>
<td>63/M</td>
<td>CT, Rt, DA</td>
<td>Not documented</td>
<td>7</td>
<td>Cerebrum</td>
<td>Surgery, DA, Rt</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
<td>8</td>
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<tr>
<td>Kasantikul, 1993</td>
<td>30/F</td>
<td>DA</td>
<td>No mitotic figures</td>
<td>7</td>
<td>Pons, subarachnoid space</td>
<td>–</td>
<td>No mitotic figures</td>
<td>Pneumonia, duodenal ulcer, deep vein thrombosis left leg</td>
<td>0.17</td>
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<td></td>
<td>22/M</td>
<td>CT, Rt</td>
<td>Benign</td>
<td>3</td>
<td>Optic nerves</td>
<td>CT</td>
<td>Mitotic figures in large numbers</td>
<td>No mitotic figures</td>
<td>–</td>
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<td>Walker, 1993</td>
<td>32/M</td>
<td>TSS, DA, TSS(4x), CT</td>
<td>No mitotic figures</td>
<td>5</td>
<td>Sphenoidal and ethmoidal sinuses, orbit, liver, lungs, hilar nodes</td>
<td>Chemo, TSS, 125I implantation, TSS, DA, Octreotide, TSS, RT, Chemp</td>
<td>No mitotic figures</td>
<td>Pneumonia</td>
<td>9.5</td>
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<td></td>
<td>48/F</td>
<td>Rt, DA, TSS</td>
<td>No mitotic figures</td>
<td>15</td>
<td>Vertebral, sacroiliac joints, femur</td>
<td>DA, RT, chemo</td>
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<td>Renal failure</td>
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<td>49/M</td>
<td>CT, Rt</td>
<td>Benign</td>
<td>2</td>
<td>Mediastinal lymph node, lung</td>
<td>DA, CT, RT, Octreotide</td>
<td>No mitotic figures</td>
<td>Pulmonary embolus post-operatively after hip replacement</td>
<td>3.5</td>
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<tr>
<td>Long, 1994</td>
<td>70/M</td>
<td>TSS</td>
<td>No mitotic figures</td>
<td>6</td>
<td>Cerebrum</td>
<td>CT, RT, CT, RT, DA</td>
<td>No mitotic figures</td>
<td>Still alive at publication</td>
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<tr>
<td>Author, year of publication</td>
<td>Age/sex</td>
<td>Primary treatment</td>
<td>PA primary tumor</td>
<td>Time interval diagnosis – metastases (years)</td>
<td>Metastatic sites</td>
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<td>Cause of death</td>
<td>Time interval diagnosis – death (years)</td>
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<td>O’Brien, 1995</td>
<td>48/M</td>
<td>CT, Rt, DA</td>
<td>Benign</td>
<td>5</td>
<td>Cerebrum</td>
<td>CT</td>
<td>Mitoses frequent</td>
<td>Still alive at publication</td>
<td></td>
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<tr>
<td>Gollard, 1995</td>
<td>33/F</td>
<td>TSS, DA, TSS biopsy, Rt</td>
<td>No mitotic figures</td>
<td>12</td>
<td>Cheek pouch, cerebrum, pelvis, ovaries</td>
<td>DA, surgery, Rt, hysterectomy, salpingo-oophorectomy, chemo</td>
<td>Mitosis 1–3/HPF</td>
<td>Still alive at publication</td>
<td></td>
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<tr>
<td>Saeger, 1995</td>
<td>59/M</td>
<td>DA, TSS(2x), Rt</td>
<td>Mitotic figures</td>
<td>5</td>
<td>Liver</td>
<td>Chemo, DA</td>
<td>Pleomorphicc</td>
<td>Pulmonary embolus</td>
<td>6</td>
</tr>
<tr>
<td>Rockwell, 1996</td>
<td>50/M</td>
<td>TSS, CT, Rt, DA</td>
<td>Benign</td>
<td>16</td>
<td>Spinal intradural</td>
<td>Gamma-knife radiosurgery, LT, RT, DA</td>
<td>Mitotic figures</td>
<td>Still alive at publication</td>
<td></td>
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<tr>
<td>Bayindir, 1997</td>
<td>32/F</td>
<td>DA, TSS</td>
<td>Mitoses and necroses, pleomorphic</td>
<td>0.08</td>
<td>Oculomotor nerve, the optic foramen, encasement carotid artery, cerebrum, spinal cord</td>
<td>CT, LT, CT</td>
<td>Mitoses and necroses</td>
<td>Death due to disease progression</td>
<td>0.25</td>
</tr>
<tr>
<td>Hurel, 1997</td>
<td>49/F</td>
<td>TSS, Rt, DA</td>
<td>Benign, p53 positive</td>
<td>5</td>
<td>Ethmoidal sinuses, orbita, temporal fossa, pons, maxillary antrum, submandibular node</td>
<td>CT, RT, DA, Ocreotide, chemo</td>
<td>Pleomorphic, p53 positive, Ki-67 positive</td>
<td>Tumor infarction or hemorrhage, coma</td>
<td>7</td>
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<td>Pernicone, 1997</td>
<td>44/F</td>
<td>TSS, Rt</td>
<td>Not documented</td>
<td>3</td>
<td>Oral submucosa, ovaries, myometrium, pelvic nodes</td>
<td>Surgery, RT, chemo, DA</td>
<td>Not documented</td>
<td>Still alive at publication</td>
<td></td>
</tr>
<tr>
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<td>34/M</td>
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<td>Not documented</td>
<td>3</td>
<td>Vertebrae, femur</td>
<td>RT</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
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<td>62/M</td>
<td>CT, Rt</td>
<td>Not documented</td>
<td>3</td>
<td>Cerebellum</td>
<td>RT, DA, Surgery</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
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<td>54/F</td>
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<td>Not documented</td>
<td>1</td>
<td>Spinal subarachnoid</td>
<td>RT, DA, chemo</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>37/M</td>
<td>TSS(2x)</td>
<td>Not documented</td>
<td>6</td>
<td>Lymph nodes</td>
<td>RT</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
<td>3</td>
</tr>
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<td>64/M</td>
<td>TSS</td>
<td>Not documented</td>
<td>6</td>
<td>Occipital lobe, tentorium</td>
<td>Unknown</td>
<td>Not documented</td>
<td>Still alive at publication</td>
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<td>Popadic, 1999</td>
<td>51/M</td>
<td>CT, DA, Rt</td>
<td>Invasive prolactinoma, pleomorphism, no mitotic figures</td>
<td>4</td>
<td>Spinal cord</td>
<td>TSS, LT, Rt, DA</td>
<td>Pleomorphism with rare mitotic figures, tumor cells in nervous and fibrous tissue</td>
<td>Still alive at publication</td>
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<tr>
<td>Arias, 2000</td>
<td>32/M</td>
<td>DA, CT, Rt</td>
<td>Mitosis</td>
<td>1</td>
<td>Medulocerebral angle, vertebrae, spinal epidural space</td>
<td>CT, Rt</td>
<td>Mitosis; tumor cells in subarachnoid space and in venous blood channels</td>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Petrossians, 2000</td>
<td>43/M</td>
<td>CT, TSS(2x), DA</td>
<td>Not documented</td>
<td>7</td>
<td>Spinal cord, rib, mediastinum, femur</td>
<td>CT, Rt, DA, gamma-knife radiosurgery(4x), CT(2x), Rt</td>
<td>Not documented</td>
<td>Death due to disease progression</td>
<td>15</td>
</tr>
<tr>
<td>Sironi, 2002</td>
<td>45/M</td>
<td>TSS, CT, TSS, Rt, Sandostatin</td>
<td>Mitosis 1/20 HPF</td>
<td>9</td>
<td>Cerebrum, spinal cord</td>
<td>CT(2x), Rt</td>
<td>Mitosis 5–25/10 HPF, Ki-67 positive, pleomorphic Ki-67 &lt; 2%</td>
<td>Pulmonary embolism</td>
<td>10.42</td>
</tr>
<tr>
<td>Vaquero, 2003</td>
<td>40/M</td>
<td>CT, Rt</td>
<td>Not documented</td>
<td>14</td>
<td>Cerebrum</td>
<td>Surgery</td>
<td></td>
<td>Still alive at publication</td>
<td></td>
</tr>
<tr>
<td>Winkelmann, 2002</td>
<td>53/M</td>
<td>DA, TSS, CT, Rt</td>
<td>Pleomorphism, Ki-67 positive</td>
<td>6</td>
<td>Orbita, foramen magnum, medulla oblongata, spinal cord, vertebrae</td>
<td>DA, gamma-knife radiosurgery(2x)</td>
<td>Pleomorphic, Ki-67 positive</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Harinarayan, 2004</td>
<td>26/M</td>
<td>CT, DA</td>
<td>Benign</td>
<td>7</td>
<td>Liver, gastric, Cerebrum, skull, pulmonary hilum, nodules lungs, ribs, pelvis, spine</td>
<td>DA, Octreo Chemo, DA</td>
<td>Benign&lt;sup&gt;c&lt;/sup&gt; Mitotic figures&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamas, 2004</td>
<td>14/M</td>
<td>TSS, DA, Rt, CT</td>
<td>Benign, Pleomorphism, numerous mitotic figures</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noda, 2004</td>
<td>52/F</td>
<td>TSS, CT, Rt, DA</td>
<td>Benign</td>
<td>7</td>
<td></td>
<td>Gamma-knife radiosurgery, RT, DA LT, DA</td>
<td>Pleomorphism, Ki-67 positive&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Respiratory arrest</td>
<td>9</td>
</tr>
<tr>
<td>Uum Van, 2004</td>
<td>20/F</td>
<td>CT(2x), DA</td>
<td>Not documented</td>
<td>13</td>
<td></td>
<td></td>
<td>Low mitotic index</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Vaishya, 2004</td>
<td>55/F</td>
<td>CT, Rt, DA</td>
<td>Benign</td>
<td>10</td>
<td>Encasement internal carotis artery, sphenoid sinus</td>
<td>TSS, DA</td>
<td>Mitosis 2/10 HPF, vascular invasian, Ki-67 positive</td>
<td>Still alive at publication</td>
<td>11</td>
</tr>
<tr>
<td>Crusius, 2005</td>
<td>47/M</td>
<td>TSS, CT, Rt, DA</td>
<td>Ki-67 2.80% and 4.40%</td>
<td>6</td>
<td>Cerebrum</td>
<td></td>
<td>Ki-67 4.45%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cardiac arrest</td>
<td>6.02</td>
</tr>
</tbody>
</table>
published cases was highly variable, with a median duration of 7 years, but ranging from 1 month to 20 years. Local recurrence after adenomectomy followed by repeated surgical interventions for local regrowth and extension of the pituitary tumor is frequently observed in malignant prolactinoma. Symptoms of prolactin hypersecretion rarely dominated the clinical picture of metastatic disease. However, symptoms of local compression at the metastatic sites were present in 73% of the cases. In some cases, metastases only manifested during autopsy (14, 18, 20, 21).

Intracranial metastases were reported in the frontal lobe (7, 9, 12, 18, 19, 22, 23, 27, 33, 34), parietal–occipital lobe (6, 22, 29), temporal lobe (10, 18, 24, 28, 33), cerebellum (4, 8, 12, 14, 29, 38), cerebello-pontine angle (5, 18, 31), brainstem (17, 20, 28, 38), and subarachnoid space (9, 14, 20). Less commonly involved areas were the cranial nerves (20, 27) and the orbital space (15, 18, 28, 35). Extracranial metastases within the central nervous system involved the spinal cord (8, 11, 13, 14, 17, 26, 27, 29, 30–33, 35, 38, 39). Approximately 40% of the malignant prolactinomas were associated with systemic metastases in bone (10, 16, 21, 29, 32, 35, 37), lymph nodes (18, 21, 28, 29, 31, 37), lung (13, 16, 21, 31, 37), liver (21, 25, 31, 36), and, rarely, ovaries (24, 29).

Treatment of metastatic disease consisted of surgery in 69%, radiotherapy in 54%, and chemotherapy in 21% of cases. There is a case-to-case variability of the effect of chemotherapy on prognosis. At publication, three out of ten patients were still alive. Survival time of the remaining seven patients after being diagnosed with metastases was 2.1 years compared with 1.9 years for the whole cohort of patients. The mean time interval of diagnosis until death was 7.8 years compared with 8 years in all reported cases. Although, these data involve only a limited number of cases, we conclude that chemotherapy does not improve prognosis of malignant prolactinoma. In addition, 60% of the patients were treated with dopamine agonists. Only a minority of the patients was treated with octreotide (8, 21, 28, 36) or gamma-knife radiosurgery (26, 32, 35, 38). Survival in these patients was not different from the other patients.

Histological investigation of the metastatic lesions showed more often tissue with atypical parameters, compared with the results obtained from the primary tumor. Atypical features were present in 62% in the metastatic lesions versus 40% in the primary tumor.

The prognosis of malignant prolactinoma is poor. Survival after the onset of initial symptoms of prolactinoma is approximately 8 years, although there are patients who have survived for as long as 25 years. Only 60% of reported cases with a prolactin-secreting pituitary carcinoma survive more than 1 year after the development of metastases. It is presently difficult to estimate long-term survival in all patients since long-term follow-up has not been reported in most of these patients.

Table 1 Continued

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Age/sex</th>
<th>Primary treatment</th>
<th>Time interval diagnosis – metastases (years)</th>
<th>Cause of death</th>
<th>Metastatic sites</th>
<th>Treatment of metastases</th>
<th>Time interval diagnosis – death (years)</th>
<th>Primary tumor</th>
<th>PA primary tumor</th>
<th>Metastatic sites</th>
<th>Treatment of metastases</th>
<th>Cause of death</th>
<th>Time interval diagnosis – death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kars, 2006</td>
<td>62/F</td>
<td>DA, CT, RI</td>
<td>3.5</td>
<td>No mitotic figures, Ki-67 10-15%</td>
<td>Sinus sphenoidales, encasement internal carotid artery, spinal cord, vertebrae</td>
<td>LT, RI(3x) Mitosis 6/HPF, Ki-67 positive</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Malignant prolactinoma: a review
Another feature indicative of a non-benign clinical course is the disappearance of prolactin-suppressive effects of treatment with DA. DA resistance, or an escape to the prolactin-suppressive effects, during treatment of prolactinoma is rare, but has been reported in the majority of patients with malignant prolactinomas (Table 3). Only six patients, however, including our case, were treated with cabergoline. When non-compliance is ruled out, this phenomenon is associated with dedifferentiation of the tumor and thus of malignant transformation. In our case, it is certainly remarkable because we found positive visualization of the pituitary tumor and the metastases by the epidepride scan (Fig. 5). Apparently, the tumor still expressed the D2 receptors because [123I] epidepride binds with high affinity to dopamine D2 receptors (46). Epidepride scintigraphy was only performed in our case and one previously reported case by Petrossians, et al. (32). Scintigraphy in the latter detected metastases in the spine, rib, mediastinum, and right femur. The metastases were treated with radiotherapy. In general, it is currently unclear how to translate these results in only two patients to the diagnostic value of this procedure in benign and malignant prolactinomas. The development of pituitary insufficiency within a time frame of several weeks is also consistent with tumor dedifferentiation and growth. The occurrence of pituitary insufficiency within such a short time interval is exceptional in pituitary adenoma.

In conclusion, malignant prolactinoma can present with unusual and atypical clinical manifestations. In the case of an invasive macroprolactinoma, these features, together with the development of resistance to dopamine agonists, should prompt the clinician to obtain histological information. In the presence of atypical indices, such as nuclear pleomorphism, numerous mitosis, and increased Ki-67 labeling index, the prolactinoma could be termed atypical to denote the potential of malignant transformation.

References


Table 2 Summary of clinical features of malignant prolactinoma presented between 1981 and 2005.

<table>
<thead>
<tr>
<th>n = 48</th>
<th>Primary tumor</th>
<th>Metastases</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Age, years</td>
<td>43.6 (range 14–70 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most prevailing symptomatology, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>17 (35)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Local compression</td>
<td>34 (71)</td>
<td>35 (73)</td>
<td></td>
</tr>
<tr>
<td>Metastatic sites (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracranial</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extramedullary</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time interval diagnosis – metastases (years)</td>
<td>6.9 (range 1 month–20 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time interval metastases – death (years)</td>
<td>1.9 (range 1 week–8 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time interval diagnosis – death (years)</td>
<td>8.0 (range 2 months–25 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive at publication (%)</td>
<td></td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

The metastases were treated with radiotherapy. In general, it is currently unclear how to translate these results in only two patients to the diagnostic value of this procedure in benign and malignant prolactinomas. The development of pituitary insufficiency within a time frame of several weeks is also consistent with tumor dedifferentiation and growth. The occurrence of pituitary insufficiency within such a short time interval is exceptional in pituitary adenoma.

Table 3 Histological, biochemical and therapeutic characteristics of the primary pituitary tumor and metastases.

<table>
<thead>
<tr>
<th>n = 48, number (%)</th>
<th>Primary tumor</th>
<th>Metastases</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological classification</td>
<td>18 (37)</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>19 (40)</td>
<td>30 (62)</td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>11 (23)</td>
<td>10 (21)</td>
<td></td>
</tr>
<tr>
<td>Response to DA</td>
<td>15 (31)</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>DA resistance</td>
<td>2 (13)</td>
<td>13 (87)</td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td>25 (52)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>21 (84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA escape</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>46 (96)</td>
<td>33 (69)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>38 (79)</td>
<td>26 (54)</td>
<td></td>
</tr>
<tr>
<td>Surgery and radiotherapy</td>
<td>38 (79)</td>
<td>20 (42)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1 (2)</td>
<td>10 (21)</td>
<td></td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>31 (65)</td>
<td>29 (60)</td>
<td></td>
</tr>
</tbody>
</table>

DA, dopamine agonists.
