Prolactinomas : clinical studies

Kars, M.

Chapter 6

MALIGNANT PROLACTINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

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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.

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

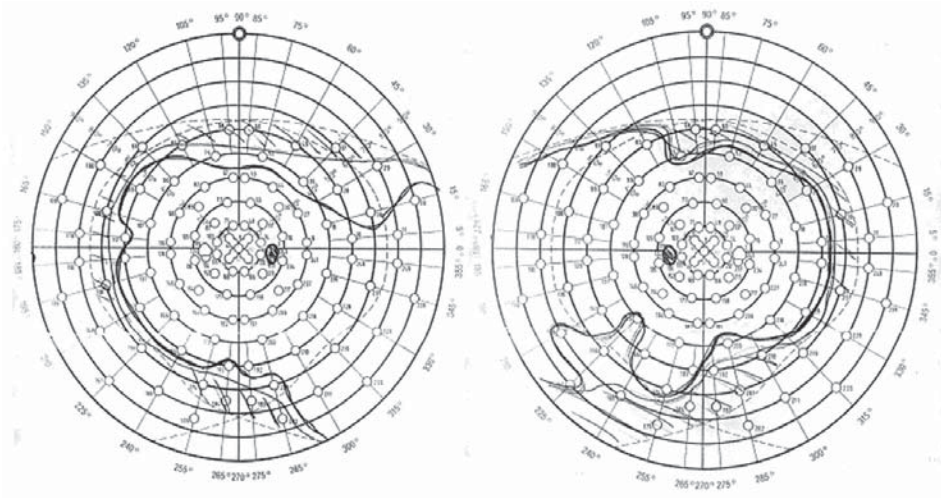

Figure 1.
Visual field investigation in October 1999, revealing bitemporal hemianopsia.

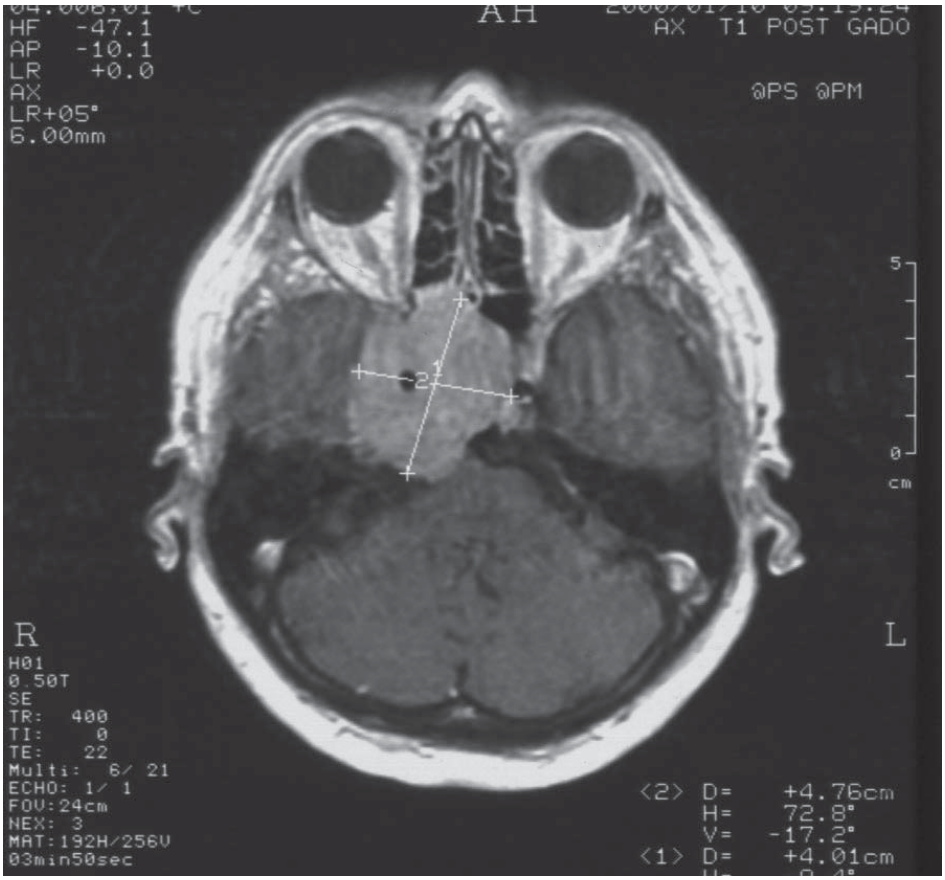

Figure 2.

MRI (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.

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 into 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), six 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* ACTH and TSH

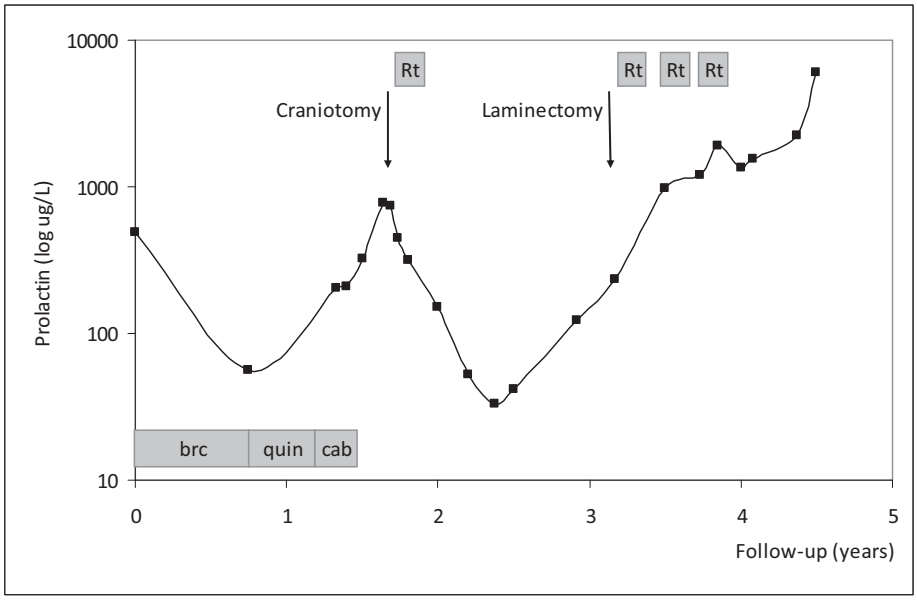

Figure 3.
Serum prolactin concentrations from October 1998 to April 2003 (normal value < 22 µg/L).
Brc, bromocriptine; quin, quinagolide; cab, cabergoline; Rt, radiotherapy.

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 of 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 x 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.

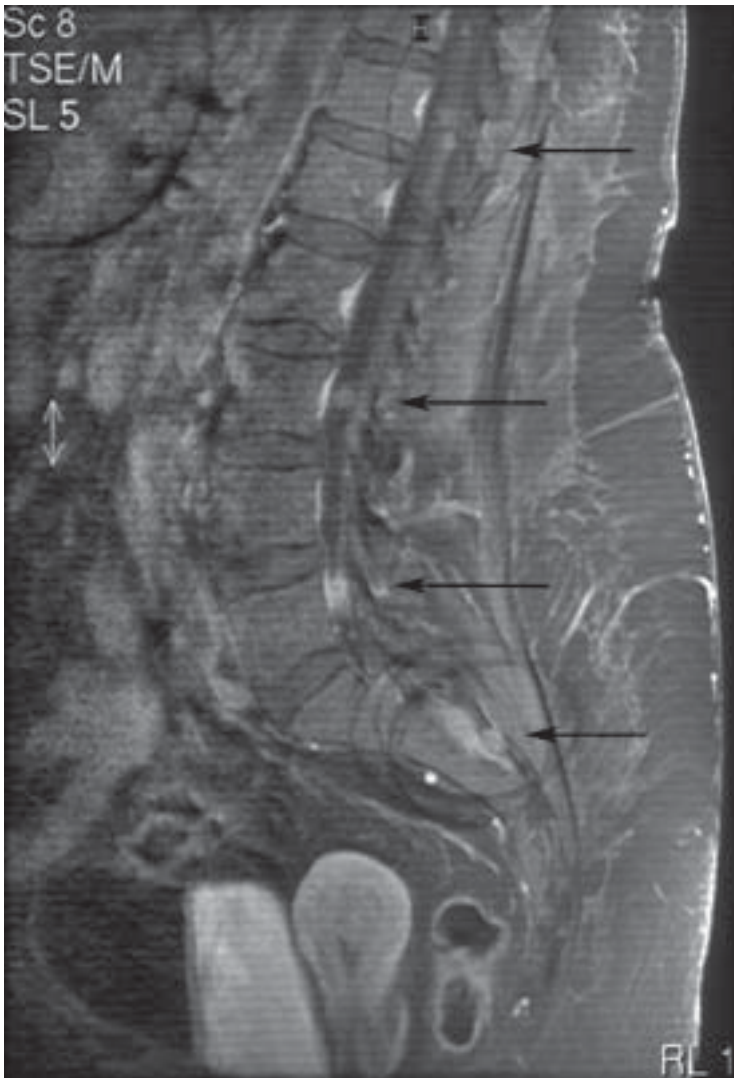

Figure 4.
MRI (sagittal T1-weighted image) obtained in November 2001, demonstrating spinal lesions (arrows) in the lumbar and sacral region.

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 in only partial improvement of visual disturbances. However, prolactin concentrations continued to increase (Fig.3) to a final prolactin concentration of 6000 µg/L in May 2003, 1 month before she died at home. Autopsy was not performed.

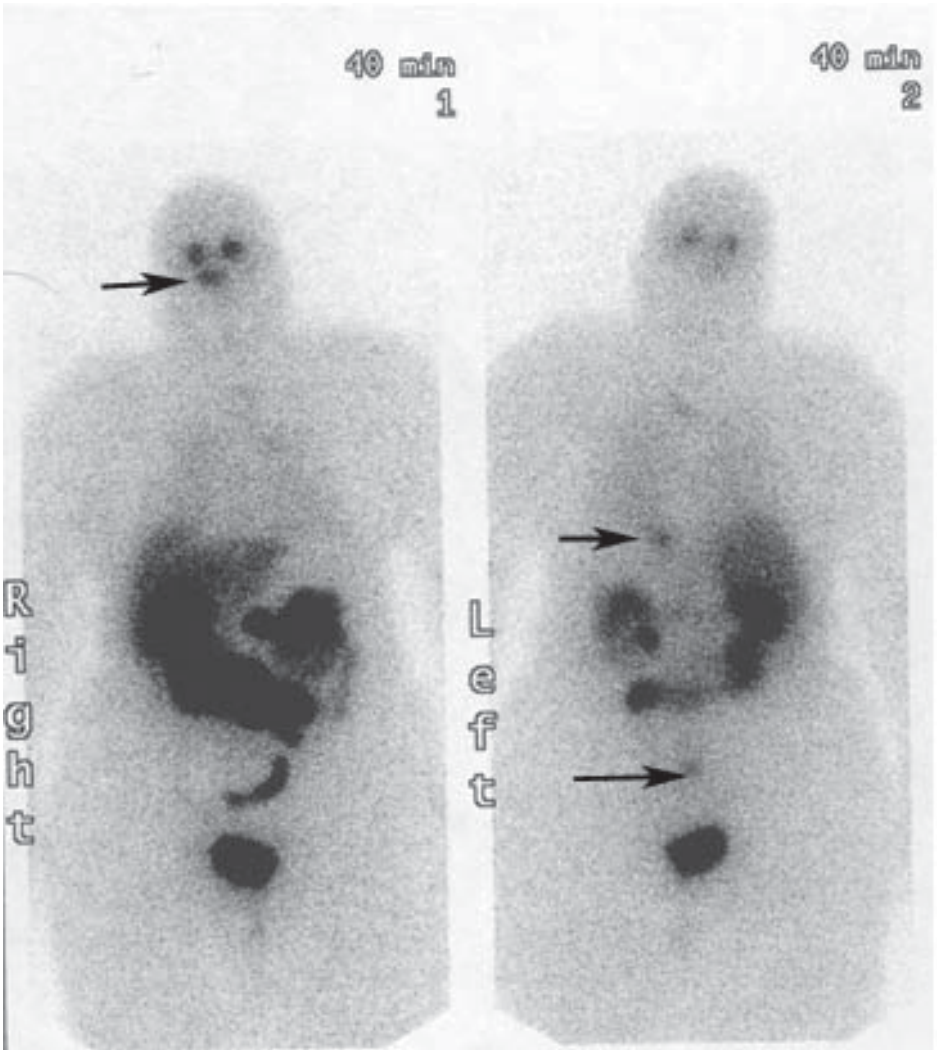

Figure 5.
Total-body scintigraphy after [^{123}I] epidepride injection in December 2001. Physiological accumulation of activity in basal ganglia, liver, kidneys, bowel, and urinary bladder. Anterior view (left image): intracranial accumulation of the isotope reflecting the macroprolactinoma (arrow). Posterior view (right image): multiple accumulations of the isotope reflecting multiple metastases in the spine (arrows).

DISCUSSION

Pituitary carcinomas are considered to arise from the transformation of initially large, but benign adenomas (1). This notion is based on observations that 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 the 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 a 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 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 hemianopsia. 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 suggestive for 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, and only 2 of these also 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 behaviour of pituitary tumors (1;3). Histological parameters associated with an atypical or aggressive behaviour 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 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 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).

Table 1. List of previously published cases of malignant prolactinoma

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Martin, 1981	31/F	TSS, Rt, CT, DA, Rt	Pleomorphism, rare mitotic figures	5.5	Cerebellum	CT	Numerous mitotic figures	Death due to disease progression	8.5
Cohen, 1983	70/M	-	No mitotic figures †	3.5	Cerebellopontine angle	-	No mitotic figures †	Pulmonary oedema, circulatory shock	3.58
U, 1984	63/M	CT, Rt	Mitosis 3/20 HPF	6	Cerebrum	CT, Rt, DA	Mitosis 11/20 HPF, pleomorphic	Pulmonary embolus	6.25
Gasser, 1985	28/M	CT, Rt, DA	Mitosis, pleomorphism	9	Cerebrum	CT, DA, Rt, CT	Mitosis, pleomorphism; tumor cells in subarachnoidal space and in venous blood channels	Death due to disease progression	12
Landgraf, 1985	44/F	CT, Rt, DA	Benign	4	Cerebellum, spinal cord	LT, Rt, DA, Chemo, Octapeptide-somatostatin, Chemo	Benign	Death due to disease progression	5.5
Plangger, 1985	28/M	CT, Rt	Benign	9	Cerebrum, subarachnoid nodules	CT, DA, Rt, CT	Mitotic figures rare	Still alive at publication	
Scheithauer, 1985	52/F	Rt, CT, TSS(2x), DA	Mitotic figures rare	11	Cerebrum, vertebrae, occipital bone, ribs	DA, Rt(2x)	Mitotic figures rare ‡	Death due to disease progression	13.5
Von Werder, 1985	43/F	CT, Rt, DA	Not documented	4	Spinal cord	DA, LT, Rt, DA	Not documented	Unknown	
Muhr, 1988	14/M	CT, Rt	Benign	12	Cerebellum, frontal lobe	Surgery, DA	Mitosis	Still alive at publication	
Atienza, 1991	34/M	DA, CT(2x), Rt, DA	No mitotic figures	4	Spinal cord, pulmonary nodules	DA, Rt, TSS	Mitosis 2/10 HPF, vascular invasion	Death due to disease progression	5.5
Popovic, 1991	47/M	DA, CT(2x), Rt	Mitosis 6/HPF	2	Dura, cerebrum, cerebellum	CT	Mitosis 6/HPF	Gastrointestinal bleeding	2.02
	56/F	TSS, Rt	Mitosis 5/10 HPF	12	Roof fourth ventricle, cerebrum, spinal cord	CT	Mitosis 5/10 HPF	Acute pulmonary oedema, S. Aureus septicemia	12.33
Berezin, 1992	32/F	CT, Rt	Benign	20	Intraorbital	CT, enucleation left eye and retroorbital mass, Rt	Mitosis 3-4/10 HPF, pleomorphism	Anorexia, pneumonia, comatose, death due to disease progression	25
Figarella, 1992	45/M	TSS, DA, CT(2x)	Mitosis 1/2 HPF	8	Vertebrae, lung	-	Not documented	Unknown	
Kamphorst, 1992	45/M	CT, Rt, Chemo, Rt	Mitotic figures rare	13	Pons, medulla oblongata, spinal cord	-	Mitotic figures rare †	Death due to disease progression	13.02
Petterson, 1992	40/M	CT, Rt, DA	Mitotic figures	5	Encasement carotid bifurcation, retro-orbital space, cerebrum, cerebellopontine angle, nodule vertebral artery	CT, DA, CT, Chemo, CT, Chemo	Pleomorphic, invading overlying cerebral tissue	Death due to disease progression	8

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Assies, 1993	63/M	CT, Rt, DA	Not documented	7	Cerebrum	Surgery, DA, Rt	Not documented	Death due to disease progression	8
Kasantikul, 1993	30/F	DA	No mitotic figures †		Pons, subarachnoid space	-	No mitotic figures †	Pneumonia, duodenal ulcer, deep vein thrombosis left leg	0.17
	22/M	CT, Rt	Benign	3	Optic nerves	CT	Mitotic figures in large numbers	Still alive at publication	
Walker, 1993	32/M	TSS, Rt, DA, TSS(4x), CT	No mitotic figures	5	Sphenoidal and ethmoidal sinuses, orbit, liver, lungs, hilar nods	Chemo, TSS, 125I implantation, TSS, DA, Octreo, TSS, Rt, Chemo	No mitotic figures	Pneumonia	9.5
	48/F	Rt, DA, TSS	No mitotic figures	15	Vertebrae, sacroiliac joints, femur	DA, Rt, Chemo	No mitotic figures ‡	Renal failure	15.5
	49/M	CT, Rt	Benign	2	Mediastinal lymph node, lung	DA, CT, Rt, Octreo	No mitotic figures	Pulmonary embolus post-operatively after hip replacement	3.5
Long, 1994	70/M	TSS	No mitotic figures	6	Cerebrum	CT, Rt, CT, Rt, DA	No mitotic figures †	Still alive at publication	
O'Brien, 1995	48/M	CT, Rt, DA	Benign	5	Cerebrum	CT	Mitoses frequent	Still alive at publication	
Gollard, 1995	33/F	TSS, DA, TSS biopsy, Rt	No mitotic figures	12	Cheek pouch, cerebrum, pelvis, ovaries	DA, surgery, Rt, hysterectomy, salpingo-oophorectomy, Chemo	Mitosis 1-3/HPF	Still alive at publication	
Saeger, 1995	59/M	DA, TSS(2x), Rt	Mitotic figures	5	Liver	Chemo, DA	Pleomorphic ‡	Pulmonary embolus	6
Rockwell, 1996	50/M	TSS, CT, Rt, DA	Benign	16	Spinal intradural	Gamma-knife radiosurgery, LT, Rt, DA	Mitotic figures	Still alive at publication	
Bayindir, 1997	32/F	DA, TSS	Mitoses and necroses, pleomorphic	0.08	Oculomotor nerve, the optic foramen, encasement carotid artery, cerebrum, spinal cord	CT, LT, CT	Mitoses and necroses	Death due to disease progression	0.25
Hurel, 1997	49/F	TSS, Rt, DA	Benign, p53 positive	5	Ethmoidal sinuses, orbita, temporal fossa, pons, maxillary antrum, submandibular node	CT, Rt, DA, Octreo, Chemo	Pleomorphic, p53 positive, Ki-67 positive	Tumor infarction or hemorrhage, coma	7
Pernicone, 1997	44/F	TSS, Rt	Not documented	3	Oral submucosa, ovaries, myometrium, pelvic nodes	Surgery, Rt, Chemo, DA	Not documented	Still alive at publication	
	34/M	DA, Rt, TSS	Not documented	3	Vertebrae, femur	Rt	Not documented	Death due to disease progression	4
	62/M	CT, Rt	Not documented	3	Cerebellum	Rt, DA, Surgery	Not documented	Death due to disease progression	11
	54/F	TSS	Not documented	1	Spinal subarachnoid	Rt, DA, Chemo	Not documented	Death due to disease progression	3
	37/M	TSS(2x)	Not documented	6	Lymph nodes	Rt	Not documented	Death due to disease progression	7
	64/M	TSS	Not documented	6	Occipital lobe, tentorium	Unknown	Not documented	Still alive at publication	

Author, year of publication	Age/ Sex	Primary Treatment*	PA primary tumor	Time interval diagnosis – metastases (years)	Metastatic sites	Treatment of metastases*	PA metastases	Cause of death	Time interval diagnosis – death (years)
Popadic, 1999	51/M	CT, DA, Rt	Invasive prolactinoma, pleomorphism, no mitotic figures	4	Spinal cord	TSS, LT, Rt, DA	Pleomorphism with rare mitotic figures, tumor cells in nervous and fibrous tissue	Still alive at publication	
Arias, 2000	32/M	DA, CT, Rt	Mitosis	1	Medulocerebral angle, vertebrae, spinal epidural space	CT, Rt	Mitosis; tumor cells in subarachnoid space and in venous blood channels	Pneumonia	3
Petrossians, 2000	43/M	CT, TSS(2x), DA	Not documented	7	Spinal cord, rib, mediastinum, femur	CT, Rt, DA, gamma-knife radiosurgery(4x), CT(2x), Rt	Not documented	Death due to disease progression	15
Sironi, 2002	45/M	TSS, CT, TSS, Rt, Sandostatin	Mitosis 1/20 HPF	9	Cerebrum, spinal cord	CT(2x), Rt	Mitosis 5-25/10 HPF, Ki-67 positive, pleomorphic	Pulmonary embolism	10.42
Vaquero, 2003	40/M	CT, Rt	Not documented	14	Cerebrum	Surgery	Ki-67 < 2%	Still alive at publication	
Winkelmann, 2002	53/M	DA, TSS, CT, Rt	Pleomorphism, Ki-67 positive	6	Orbita, foramen magnum, medulla oblongata, spinal cord, vertebrae	DA, gamma-knife radiosurgery(2x)	Pleomorphic, Ki-67 positive †	Renal failure, lung oedema, death due to disease progression	7
Harinarayan, 2004	26/M	CT, DA	Benign	7	Liver, gastric	DA, Octreo	Benign ‡	Unknown	
Lamas, 2004	14/M	TSS, DA, Rt, CT	Pleomorphism, numerous mitotic figures	6	Cerebrum, skull, pulmonary hilum, nodules lungs,ribs, pelvis, spine	Chemo, DA	Mitotic figures ‡	Still alive at publication	
Noda, 2004	52/F	TSS, CT, Rt, DA	Benign	7	Cerebellum, medulla oblongata, spinal cord	Gamma-knife radiosurgery, Rt, DA	Pleomorphism, Ki-67 positive ‡	Respiratory arrest	9
Uum Van, 2004	20/F	CT(2x), DA	Not documented	13	Leptomeningeal	LT, DA	Low mitotic index	Still alive at publication	
Vaishya, 2004	55/F	CT, Rt, DA	Benign	10	Encasement internal carotis artery, sphenoid sinus	TSS, DA	Mitosis 2/10 HPF, vascular invasion, Ki-67 positive	Death due to disease progression	11
Crusius, 2005	47/M	TSS, CT, Rt, DA	Ki-67 2.80% and 4.40%	6	Cerebrum		Ki-67 4.45% ‡	Cardiac arrest	6.02
Kars, 2006	62/F	DA, CT, Rt	No mitotic figures, Ki-67 10-15%	3.5	Sinus sphenoidales, encasement internal carotis artery, spinal cord, vertebrae	LT, Rt(3x)	Mitosis 6/HPF, Ki-67 positive	Death due to disease progression	5

M, male; F, female; Chemo, chemotherapy; CT, craniotomy; DA, dopamine agonist; HPF, high-powered field; LT, laminectomy; PA, pathological anatomic investigation; Octreo, octreotide; Rt, radiotherapy; TSS, transsphenoidal surgery.

* Number in parentheses indicate number of treatments

† Pathological findings on autopsy

‡ Pathological findings on biopsy

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

n=48		
Gender, male, *%*	65	
Age, *yr*	43.6 (range 14-70)	
Most prevailing symptomatology, *No. (%)*	*Primary tumor*	*Metastases*
Hyperprolactinemia	17 (35)	1 (2)
Local compression	34 (71)	35 (73)
Metastatic sites, *%*		
Intracranial	75	
Extracranial	33	
Extramedullary	40	
Mean time interval diagnosis – metastases, *yr*	6.9 (range 1 month -20 years)	
Mean time interval metastases – death, *yr*	1.9 (range 1 week – 8 years)	
Mean time interval diagnosis – death, *yr*	8.0 (range 2 months – 25 years)	
Alive at publication, *%*	29	

Data are expressed as mean, unless otherwise mentioned. Yr, year.

The time interval between the onset of symptoms at presentation and subsequent metastases in the 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;29-33;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 is 7.8 years compared with 8 years of 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.

Another feature indicative for 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 visualisation of the pituitary tumor and the metastases by the epidepride scan (Fig.5). Apparently, the tumor still expressed the D2 receptors because [^{123}I] epidepride binds with high affinity to dopamine D2 receptors (46). Epidepride scintigraphy was only performed in our case and in only one previously reported

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

n=48	Primary tumor	Metastases	Overall
Histological classification			
Typical	18 (37)	8 (17)	
Atypical	19 (40)	30 (62)	
Not documented	11 (23)	10 (21)	
Response to DA			
DA resistance			15 (31)
Cabergoline			2 (13)
Others			13 (87)
DA escape			25 (52)
Cabergoline			4 (16)
Others			21 (84)
Therapy			
Surgery	46 (96)	33 (69)	
Radiotherapy	38 (79)	26 (54)	
Surgery and radiotherapy	38 (79)	20 (42)	
Chemotherapy	1 (2)	10 (21)	
Dopamine agonist	31 (65)	29 (60)	

Data are expressed as number (percentage). DA, dopamine agonist.

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.

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