รายงานผู้ป่วย

Intracranial metastases from prolactin-producing pituitary carcinoma

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A rare case of a patient with intracranial metastases from a pituitary carcinoma is described. The patient had been operated on for a pituitary adenoma in 1978. She presented 16 years later with headache and visual disturbance, at which time magnetic resonance imaging scans revealed local recurrence and frontal and cerebellar metastases. The serum prolactin level was elevated and a histopathologic examination showed pituitary neoplastic cells with positive immunostaining for prolactin. Metastatic spread of pituitary carcinomas within the central nervous system is briefly reviewed.

Key words : *Pituitary carcinoma, Prolactinoma, Metastases.*

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ได้รายงานผู้ป่วยที่มีการแพร่กระจายภายในสมองจากเนื้องอกต่อมใต้สมอง ซึ่งพบได้น้อย โดยที่ผู้ป่วยได้รับการผ่าตัดเนื้องอกต่อมใต้สมอง ตั้งแต่ปี พ.ศ. 2521 16 ปีต่อมาผู้ป่วยมีอาการปวดศีรษะร่วมกับการมองเห็นที่ผิดปกติ จาก MRI พบว่า มีเนื้องอกต่อมใต้สมอง ร่วมกับเนื้องอกบริเวณสมองส่วนฟรอนทรัล และซีรีเบลลั่ม ผลการตรวจทางโลหิตวิทยาพบว่ามีระดับฮอร์โมนโปรเลคทินสูงขึ้น และจากผลการตรวจชิ้นเนื้อทางพยาธิวิทยาเข้าได้กับเนื้องอกต่อมใต้สมอง ซึ่งผลิตฮอร์โมนโปรเลคทิน รายงานนี้ได้ทำการทบทวนการแพร่กระจายภายในสมองจากเนื้องอกต่อมใต้สมองไว้อย่างสั้นๆ

Pituitary adenomas are usually benign tumors, although sometimes they grow invasively, and malignant forms with metastases are rare. Pituitary carcinomas with metastases have been described in only a few cases and prolactin-producing pituitary adenoma (prolactinoma) with metastases are extremely rare.[1-8] We report here a case of 39 year old woman who was diagnosed with prolactinoma at craniotomy, and 17 years later had local recurrence and multiple metastases. The literature on metastatic pituitary carcinoma is also briefly reviewed.

Case report

A 39 year old woman developed secondary amenorrhea with visual disturbances in 1978. She had a right subfrontal craniotomy for resection of the pituitary adenoma followed by cranial irradation. Histopathological examination determined chromophobe adenoma but immunostaining was not available at that time. She had been well until July 1994 when whe developed headaches and visual disturbances. On physical examination, she was found to have bitemporal hemianopsia and amenorrhea. Other nueurological findings were normal An MRI scan of the brain showed widening of the sellar turcica occupied by mixed solid and cysic masses with suprasellar extension causing pressure on the optic chiasm, and two mixed solid and cystic masses at the right frontal lobe and the cerebellum. (Fig.1) Endocrinological testing revealed that PRL level was 428 ng/ml (normal, less than 25 ng/ml) Thyroxine level was 2 μg/dl (normal,6-12 μd/dl), Triiodothyronine level was 40 ng/dl (normal,80-180 ng/dl) and TSH level was 0.03 IU/ml (normal, 0.5-4 IU/ml). Other hormones level was unremarkable.

The patient underwent a suboccipital craniectomy for removal of the tumor at the cerebellum on Febuary 20, 1995. As a second step, a right frontotemporal craniotomy was carried out on Febuary 27, 1995 for removal of the tumor at the right frontal lobe and sellar region. The tumor was extensively removed but a part of the tumor which was in sellar turcica was left behind.

Postoperatively, the patient was well and the visual field improved. The patient had been followed by whole brain irradiation to a total dose of 30 Gy with booster dose at frontal region to 45 Gy. With 2 1/2 years followed- up peroid, the patient is feeling well and working full-time and headache has ceased.

Histopathological finding

The lesion from the pituitary gland, frontal lobe and cerebellum were fixed in 10% formaldehyde solution. Paraffin sections were stained with hematoxylin and eosin (H&E). The peroxidase-antiperoxidase method using antibodies to prolactin, growth hormone, adenocorticotrophic hormone, follicle-stimulating hormone, luteinizing hormone and thyroid-stimulating hormone was done in formalin fixed and paraffin-embedded tissue sections.

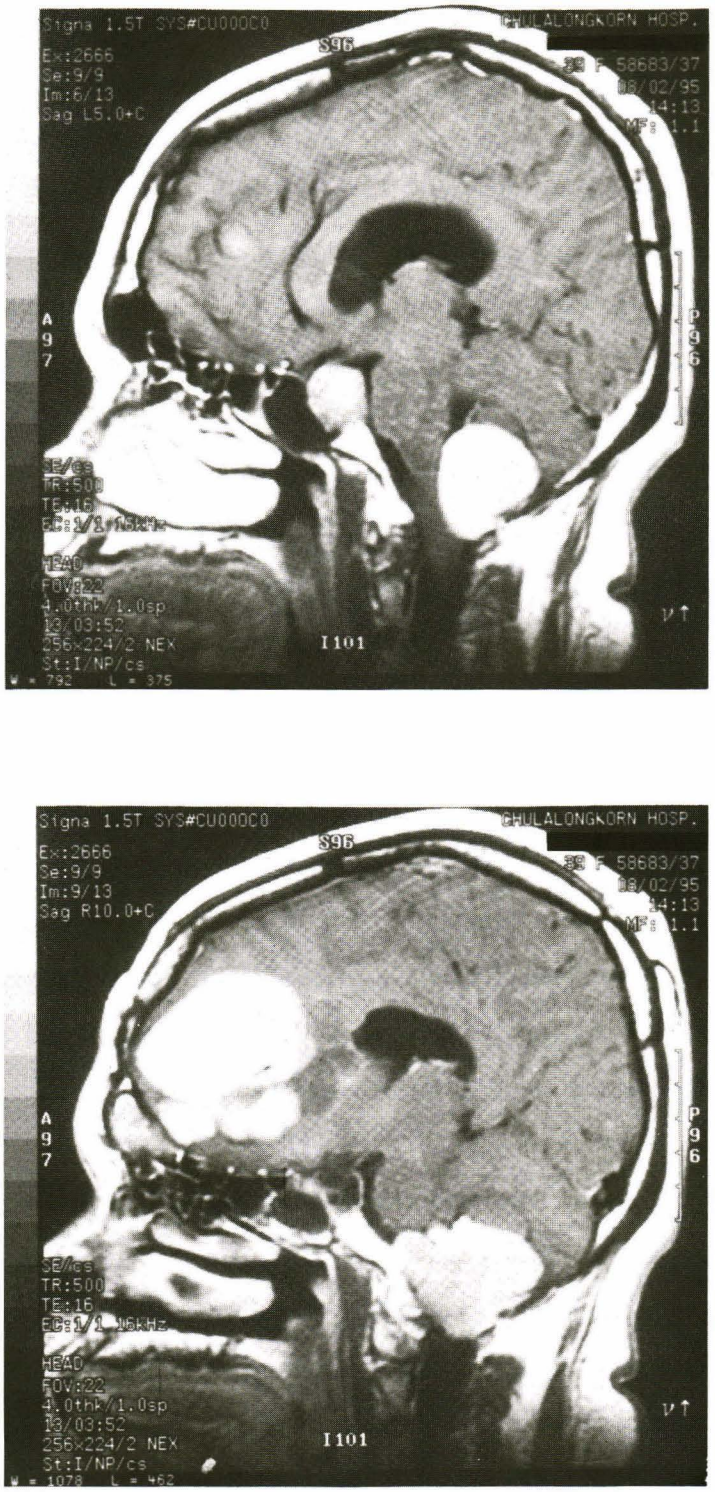

Figure 1. Magnetic resonance images demonstrate prolactinoma metastases in the frontal lobe and the cerebellum with local recurrence in sella turcica (A and B)

Microscopically, the tumor cells obtained from the pituitary gland at the first operation were chromopholic with regular oval nuclei. These polygonal cells arranged in sheets and sinusoidal pattern (Fig 2A). The tumor cells were shown to contain prolactin (Fig 2B). Sections taken from the frontal lobe and the cerebellum demonstrated a similar histological findings. However, the tumor cell had invaded the brain parenchyma and were in the subarachnoid space (Fig 3A). Additionally, nuclear pleomorphism and multinucleated cells were also noted (Fig 3B). Immunostainings were positive for prolactin but negative for other pituitary hormones (Fig 3C)

Discussion

In this case, intracranial metastatic pituitary carcinoma was associated with heper-prolactinemia. Prolactin-producing pituitary adenom (Prolactinoma) rarely exhibits aggres-sive growth. The metastatic features of this case illustrate the potential malignancy of these lesions and underscore the need for an aggressive treatment and follow-up of prolactinomas.

Adenomas arising from the anterior lobe of the pituitary gland are symptomatic as a result of their secretory activities or their expansive growth.[9] These lesions are generally regarded as benign even though mitotic figures are not

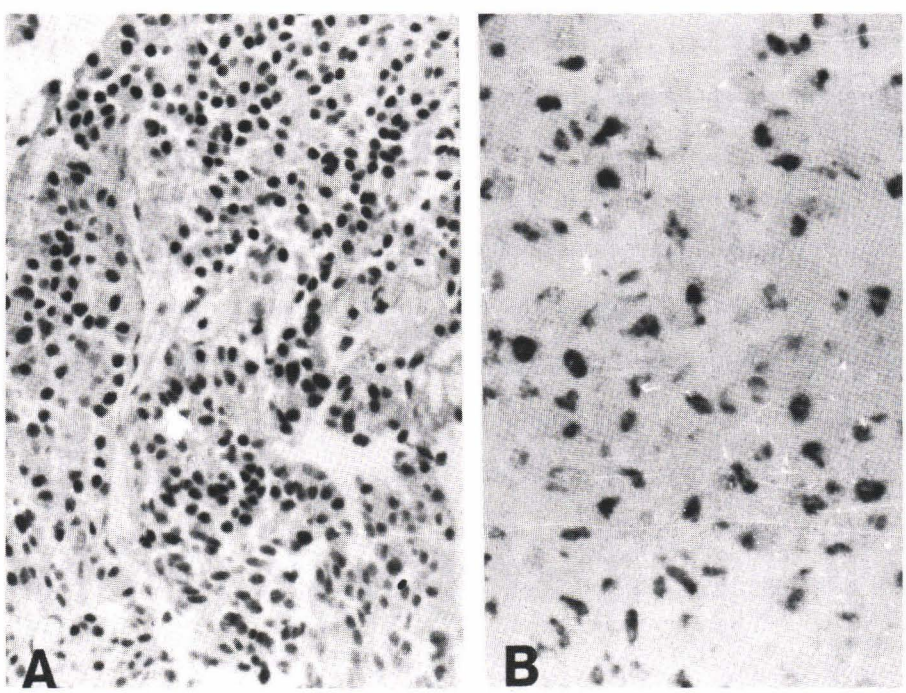

Figure 2A. Photomicrographs of the pituitary tumor removed at the first craniotomy show benign chromophobic cells (H & E x 200)

2 B. Immunohistochemical reactive prolactin is present in the cytoplasm of tumor cells (Immunostain x 400)

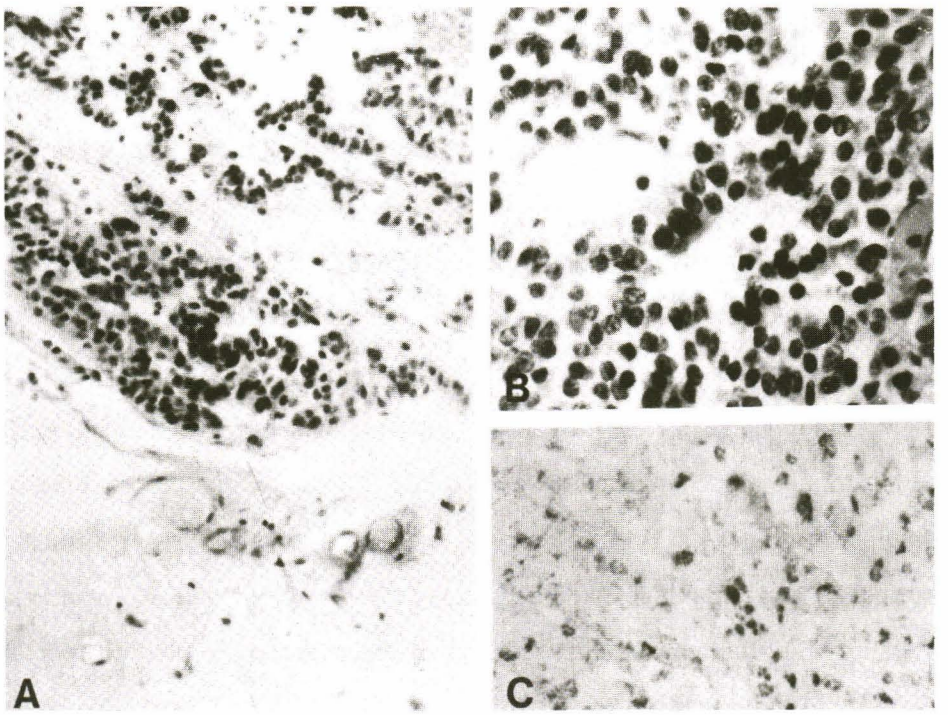

Figure 3 A. Photomicrographs of the cerebral tumor removed at the second operation show tumor cells in subarachnoid space (H & E x 200)

3 B. Higher power view demonstrates nuclear pleomorphism (H & E x 400)

3 C. Immunostain shows positive for prolactin. (Immunostain x 400)

uncommon.[10] There is, in fact, an inconsistent correlation between histological appearance and malignancy in pituitary adenomas. Noninvasive pituitary adenomas, like benign endocrine tumor of the other types, may show cellular pleomorphism and significant mitotic activity but there are several reports of distant metastases originating from histological benign pituitary adenoma.[11-13] Landolt,[14] in an electron microscopy study, found no distinct ultrastructural differences between invasive and noninvasive adenomas. It seems appearant that biological behavior, rather than histopathological criteria, establishes the diagnosis of malignancy in pituitary adenomas.

Most reported pituitary carcinomas have been either hormonally inactive or associated with Cushing disease or acromegally.[15] Only 13 cases of metastatic prolactinomas were reported with deposit in the frontal lobe,[1,4] the occipital lobe,[8] para/suprasellar region,[16] the cerebellum,[6] the cerebellopontine angle,[4] multiple intracranial metastases[3,5,17,18] and extracranial metastases.[2,7,19] The time interval between the diagnosis of primary pituitary adenoma and development of metastases is very variable[1,3,4,8,16,20] and can extend up to 20 years.[16] All of publised cases are summarized in Table 1.

In general, metastases within the central

Table 1. List of published cases of metastatic prolactin-producing pituitary carcinoma

References	Patients			Site (s) of Metastases	Surgery on Pituitary tumor[c]	Radiotherapy before Diagnosis of Metastases	Bromocritine Response	Survival after Diagnosis of Carcinoma	Outcome
	Sex	Age[a]	Latency (yr.)[b]						
6	F	31	5	Cerebellum	Transsph, Cranio	2 treatment[d]	Initial respone, but metastasis developed with bromocriptine	3 yr.	Death, progressive disease
8	M	62	6	Occipital lobe	Cranio	6 yr.	Failed preterminal trial	Weeks	Death, pulmonary embolism
4	M	70	3.5	Cerebello-pontine angle	No	No	Not used	Weeks	Death, pulmonary edema
5	F	28	9	Frontal lobe, dura	Cranio(x3)	2 treatment[e]	Erratic, Progressive disease	3 yr.	Death, progressive disease
19	F	60	A.F.	Lung, Liver, Kidney	No	No	Not used	5 days	Death, arrthymia, hypotension
7	F	64	12	Scalp, Bone-occiput, vertebrae, ribs	Cranio, Transsph	12 yr.	Good initially, but progressive disease	1 yr.	Death, progressive disease
3	M	14	12	Frontal lobe, Cerebellum	Cranio	No	Continued remission	> 12 yr.	Continued improvement radiologically
2	M	34	3	Lung, Vertebrae	Cranio	3 yr.	Initial response, but metastasis developed with bromocriptine	1 yr.	Death, progressive disease
18	M	49	2	Multiple surface nodules-dura, cerebrum, cerebellum	Cranio (x3)	8 mo.	Initial response but progressive disease	2 wk	Death, progressive disease
18	F	68	12	Roof of fourth ventricle, parasellar region, spinal cord	Transsph	12 yr.	Not used	3 mo.	Death, progressive disease
16	F	30	20	Eye, Retroorbital space	Cranio (x2)	2 treatment[f]	Erratic, progressive disease	6 yr.	Death, progressive disease

17	M	40	6	Frontal and Temporal lobe, Lateral ventricle, Cerebello-pontine angle	Cranio (x3)	6 yr.	Initial response but progressive disease	3 yr.	Death, progressive disease
1	M	48	5	Frontal lobe	Cranio	5 yr.	Initial response, but metastasis developed with bromocriptine	> 7 yr.	Continued improvement radiologically

a Age at diagnosis

b From diagnosis of adenoma to diagnosis of carcinoma

c Transsph, transsphenoidal ; Cranio, craniotomy

d At 5 years and 1 year previously

e At 12 years and 2 years previously

f At 19 years and 4 years previously

A.F. At the first diagnosis

nervous system probably result from spread of tumor cells by the cerebrospinal fluid circulation. Tumor invasion or surgical violation of the basal cisterns provides neoplastic cells with access to the subarachnoid space. Nevertheless, the hematogenous route has also been reported.[4,14,18,20]

The results of management of established metastatic pituitary carcinoma are poor. Radiotherapy, whilst effective in preventing tumor regrowth in pituitary carcinoma, was of no value in this case. 21/43 cases of metastatic pituitary ademomas had been given radiotherapy without a benificial response and this may indicate a more aggressive tumor behavior.[15] The mainstay of the treatment of prolactinoma is bromocriptine, Dapamine-agonist drug.[21] The drug has also been used in patients with metastatic lesion in the brain. The result is disappointing also. The drug did not lead to a satisfactory suppression of prolactin level or to clinical remission.[1-5] In view of the nature of the effect of bronocriptine, that is induction of cellular atrophy rather than cell death,[22] persistence of tumor and even further growth are not surprising. Further experience with bromocriptine should clarify the indication for bromocriptine as an antitumor agent.

In conclusion, metastatic pituitary carcinomas are obviously very rare, may present many years after the diagnosis of the primary pituitary adenoma. Repeated recurrence and residual tumor should be carefully followed and treated at early stage because metastases result in poor prognosis.

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