PEER REVIEWED LETTER

Pituitary Carcinoma with Subependymal Spread

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Pituitary carcinomas have been reported to metastasize systemically and, less commonly, along the craniospinal axis.[1] Metastatic lesions have been reported in the cerebral cortex, cerebellum, spinal cord, leptomeninges, cervical lymph nodes, liver, ovaries, and bone.[2] The authors are unaware of any other examples of subependymal metastases of a pituitary carcinoma. We report such a case.

Pituitary carcinoma is rare, accounting for roughly 0.2%[1,3-5] of all pituitary tumors, with approximately 140 cases reported in the literature. These tumors are associated with a very high mortality, with 66% of patients dying within the first year after diagnosis.[1,2] Pituitary carcinomas are differentiated from invasive pituitary adenomas by the presence of non-contiguous craniospinal tumor deposits and/or distant systemic metastases. The majority (88%) of these carcinomas prove to be hormone secreting, with prolactin secreting tumors being the most common.[2] Invasive carcinomas evolve from hormone secreting pituitary adenomas after a latency period. Pituitary carcinomas have a predilection for systemic spread. The rate of systemic metastasis approaches 71% for prolactin producing tumors and 57% for ACTH producing tumors.[1] Thirteen percent of tumors demonstrate both systemic and craniospinal patterns of metastatic spread.[1]

In our case, a 60-year-old man presented initially with a large prolactin secreting pituitary adenoma which was treated by partial excision followed by radiotherapy. This tumor showed no invasion into the hypothalamus or third ventricle. Ten years later he presented with multiple subependymal lesions around the lateral ventricles, the third and fourth ventricles, infiltration of the choroid plexus and enhancing intradural extramedullary nodules at levels T12 and L1.

A 60-year-old caucasian male presented in 1994 with a four month history of blurred vision in his left eye, decreased libido, failure to achieve erection and a ten-year history of mild intermittent headaches. Assessment of pituitary function revealed an elevated Prolactin level (1300 ug/L) with diminished gonadotropin and sex hormone levels (FSH 0.8IU/L and LH 0.7 IU/L, testosterone 1.8 nmols/L). An MRI of the head showed an irregular shaped mass in the pituitary fossa with suprasellar extension measuring 5cm x 3cm x 4cm. This mass was isointense in both T1 and T2 weighted images and enhanced markedly with gadolinium. There was no invasion into the hypothalamus or third ventricle. On the left side, the carotid artery was encircled by the lesion. Ophthalmologic exam showed visual acuity of 20/25 on the right and counting fingers on the left. Visual fields showed a left temporal field defect. The clinical presentation and endocrine levels suggested the diagnosis of a prolactin secreting pituitary adenoma (prolactinoma). In January 1995, he was treated by a right frontal-temporal craniotomy, as the tumor was eccentric. Only partial resection was possible as the tumor engulfed the carotid artery and extended into the cavernous sinus. Histopathological evaluation confirmed the diagnosis of prolactinoma (Figure 1). A course of radiotherapy (5040 cGys in 28 fractions over 42 days) followed. Postoperative pituitary function revealed persistent hyperprolactinemia (150 ug/L) and as a result he was started on Bromocriptine, 3.75 mg/day. He was also placed on Synthroid, Cortisone Acetate and testosterone as replacement therapy for panhypopituitarism. By January 1996, his ophthalmologic exam showed that his visual acuity had returned to 20/20 on both sides and his visual fields were normal. Also, by this time his serum prolactin level had dropped to 17ug/L allowing a reduced dose of

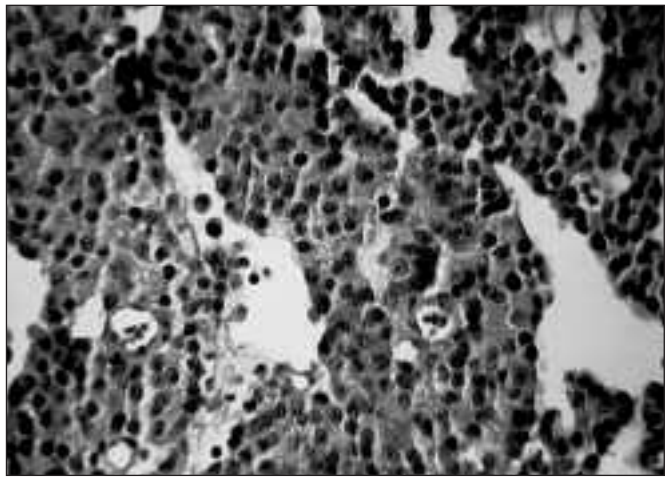

Figure 1: *The primary pituitary tumor which was resected in 1995 reveals a conventional pituitary adenoma characterized by monotonous cells with round nuclei, eosinophilic cytoplasm and no mitotic activity.*

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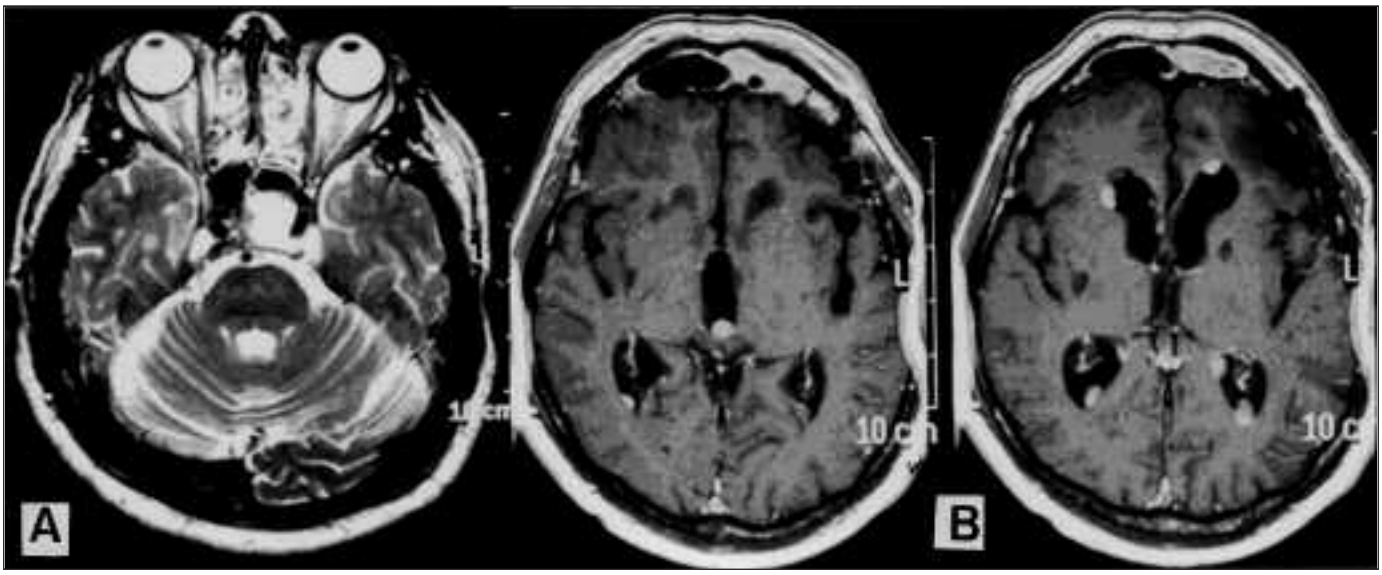

Figure 2: *(A)Axial T2 weighted MR images depicting CSF-signal filling area of previous pituitary adenoma resection. No sellar or suprasellar mass is seen. Incidental ethmoid sinusitis is present. (B) Gadolinium enhanced axial T1-weighted MR images demonstrate multiple homogeneously enhancing nodules of variable size lining the ventricular surfaces and surfaces of the choroid plexus.*

Bromocriptine to 2.5 mg/day and he became eupituitary on the hormone replacement therapy. He was followed for the first two years at six-month intervals, and yearly intervals thereafter, with full clinical assessment including CT/MRI of the head.

In mid 2004 he presented with a four-month history of positional vertigo, insomnia, diaphoresis, generalized weakness and a weight loss of 30 pounds. Prolactin levels at this time had risen to 300ug/L. An MRI of the head revealed no recurrence of tumor in the sellar/parasellar region (Figure 2a). However, multiple bilateral enhancing subependymal nodules were found lining the lateral, third and fourth ventricles and infiltrating the choroid plexus in the lateral and third ventricles (Figure 2b). Two of these nodules were larger in size, one located in the right frontal horn of the lateral ventricle and the second in the posterior part of the third ventricle. A biopsy of these lesions was offered to the patient but he declined the procedure. Repeat MRI four months later demonstrated interval growth and increase in the number of the subependymal nodules. Two intradural extramedullary enhancing nodules were now also visualized at T12 and L1. The cytological evaluation of cerebrospinal fluid (CSF) collection, performed twice, failed to find any evidence of lymphoma or malignant cells. By now his serum prolactin level had risen to 1100ug/L. In order to discern the etiology of these lesions, the patient now agreed to a frameless stereotaxic biopsy of a right frontal subependymal nodule, which was performed in April of 2005, establishing the diagnosis of pituitary carcinoma. Subsequently, the patient received a course of radiotherapy to his cerebrospinal axis (4500 cGy 25 fractions over 37 days). At present he is an in-patient on a rehabilitation unit and he is becoming cognitively impaired. He has lost an additional 25lbs in the past three months and has developed weakness of the hip flexors (grade 3 power).

The stereotaxic biopsies were fixed in 10% buffered formalin overnight, processed and sectioned by routine histological techniques after paraffin embedding. Sections were then stained with hemotoxylin and eosin.

Immunohistochemical analyses were performed on the formalin-fixed tissue. Primary antibodies were used for the following antigens: Cytokeratin, synaptophysin, GFAP, proliferation index Ki67 (MIB-1, Immunotech Inc., France;monoclonal dilution 1:100), prolactin, growth hormone, ACTH, TSH, LH and FSH. Specimen of the resected primary tumor in 1995 was reviewed and paraffin blocks were sectioned. Similar immunostains were performed on these slides.

The carcinoma biopsied in 2005 showed a small discrete nodule in the white matter just beneath the ventricular surface. Tumor cells showed round uniform nuclei, “salt and pepper” chromatin and brisk mitotic activity (Figure 3a), whereas the primary pituitary tumor resected in 1995 revealed a conventional pituitary adenoma, characterized by cells with eosinophilic cytoplasm and no mitotic activity (Figure 1).

A high proliferation index of greater than 50% was demonstrated by Ki67 in the metastatic carcinoma (Figure 3b) while the primary adenoma showed an extremely low proliferative index (1.2%). Both tumors were positive for synaptophysin. Stains for pituitary hormones revealed strong and diffuse immunoreactivity for prolactin (Figure 3c). Rare cells displayed positivity for growth hormone. The tumor cells were negative for adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH).

Data, although limited by the paucity of reported cases, demonstrates that the time interval between presentation of a sellar adenoma and metastatic disease is indeed variable,

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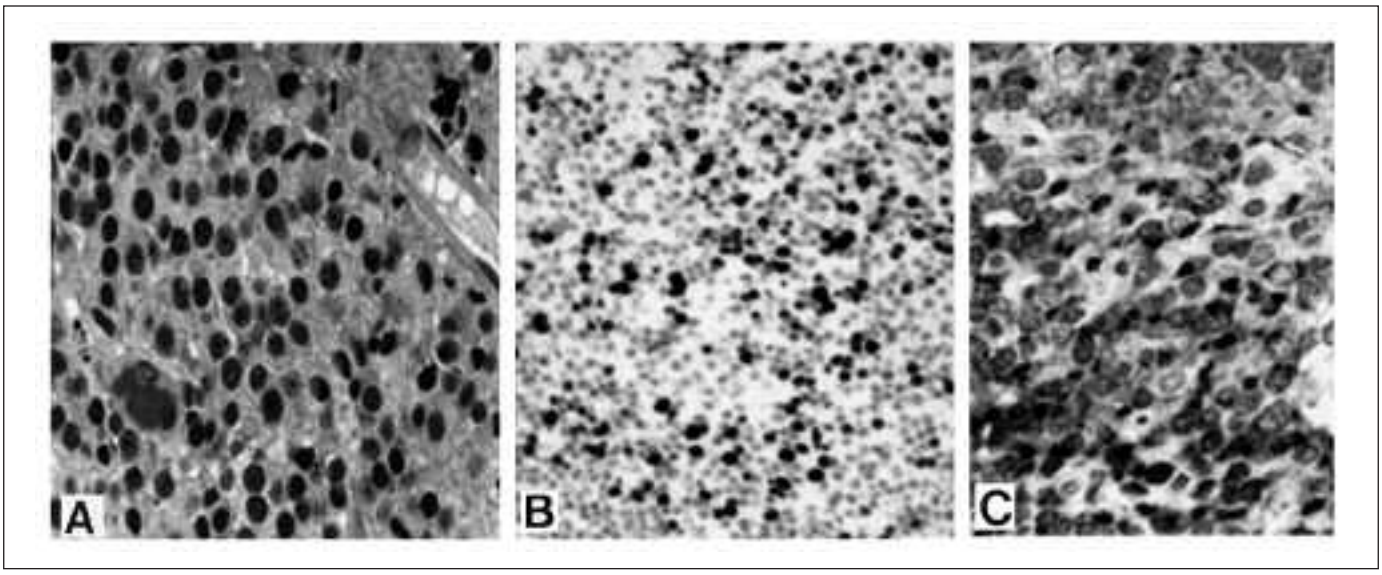

Figure 3: *(A) High magnification of the tumor nodule biopsied in 2005 reveals atypical cytological and nuclear features. The neoplastic cells demonstrate round nuclei, high N/C ratio and brisk mitotic activity. (B) A high proliferative index is illustrated by MIB – 1 (Ki67) (biopsy 2005). (C) The same pituitary hormone or prolactin is demonstrated by immunostaining.*

ranging, from several months to 18 years with a mean of 6.6 years.[1,6,7] In this case of a prolactin-secreting carcinoma the progression from diagnosis of adenoma to diagnosis of carcinoma took ten years. Prolactin secreting tumors have shown to progress more quickly to carcinoma (4.7 years) than ACTH-secreting tumors (9.5 years).[2,6] Even though metastases limited strictly to the craniospinal axis are more common with prolactin cell tumors (48%) than ACTH carcinomas (29%), both have a higher rate of systemic metastases.[1] In our case, so far, there has been only subependymal and intraspinal metastases evident. We have no clear explanation for this subependymal pattern of spread. We can only hypothesize that at the time of the initial craniotomy, some tumor cells spilled into the CSF and became deposited in the choroid plexus. Subsequent radiotherapy kept these deposits quiescent for the next ten years. The reason for the reactivation of these tumor cells after a lengthy latency period remains unexplained.

Even though many cases of pituitary carcinomas arise following pituitary adenoma, the pathogenesis of this cancer remains poorly understood. The possible causes to be considered here are: 1) The role of previous radiation in the treatment of the primary pituitary tumor, 2) microscopic tumor seeding at the time of previous surgery, 3) malignant progression of the initial pituitary tumor, 4) de novo carcinoma.

To explain the transition from benign adenoma to malignant carcinoma attempts have been made to identify certain pathological and histochemical markers of tumor aggressiveness. Features such as nuclear pleomorphism, mitotic rate, increased cellularity and even necrosis are not reliable indicators of aggressive biology as determined by growth rate, likelihood of recurrence, propensity for local invasion and capacity to metastasize.[8] That said, there is a slight trend toward greater proliferative rates, cellular activity and cellular aneuploidy in metastatic lesions compared to primary adenomas.[1] Thapar[9] used the MIB-1 monoclonal antibody, which recognizes the Ki-67 cell-cycle specific nuclear antigen, and found higher mean growth fraction in carcinomas (12%) than in both invasive (4.5%) and non-invasive (1%) adenomas.

In our case, the initial pituitary adenoma showed no cytological or histological features to suggest aggressive behavior (Figure 1). The morphological difference between the primary pituitary adenoma and metastatic carcinoma in this case is evident as illustrated in Figure 3a. The primary pituitary tumor showed benign features of a conventional adenoma, while the metastatic tumor demonstrated significant cytological atypia and brisk mitotic activity. Ki67 shows a very high labeling index of greater than 50% (Figure 3b). This indicates that many cells are going through the cell cycle and usually predicts an aggressive behavior. Although there is significant difference in terms of morphological and cytological features between the two tumors, both primary and metastatic tumors share similar immunophenotyping features. Because the site of metastases were unusual in this case, demonstration of a high serum prolactin was an important factor in diagnosis (Figure 3c).

The treatment options available in this case were: 1) surgical resection, 2) the use of dopamine agonist drugs, 3) radiotherapy and 4) chemotherapy. The surgical option was not feasible due to widespread subependymal lesions. The patient was started on Bromocriptine after initial surgical resection in 1995, but he discontinued on his own five years later. In mid 2004, Bromocriptine was restarted at a dose of 2.5 mg/day, when his serum prolactin level was discovered at 330ug/L which rose to

1100ug/L by the time diagnosis of pituitary carcinoma was established. It appears that these pituitary carcinomas "escape" dopamine suppression and therefore the palliation for such tumors is poor.

As we hoped that radiotherapy would provide some palliation, this patient received radiotherapy of the whole brain and spinal cord (4500 cGy 25 fractions over 37 days). We hope it will provide our patient a longer survival and better quality of life.

Although there are different chemotherapy protocols available the results have been disappointing.[10]

We have presented an unusual case of a pituitary carcinoma with subependymal spread, infiltration of the choroid plexus and drop metastases in the dorsolumbar area. As far as we are aware, such a spread has not been documented in the past. There is no evidence of recurrence in the sellar or parasellar regions. The treatment of these tumors remains a challenge. Radiotherapy has been given to achieve palliative benefit. The prognosis in such cases will remain poor until a better chemotherapeutic or hormonal-manipulative agent has been found.

References

1. Pernicone PJ, Scheithauer BW, Sebo TJ, Kovacs KT, Horvath E, Young WF, et al. Pituitary carcinoma: a clinicopathological study of 15 cases. Cancer. 1997; 79: 804-12.
2. Ragel BT, Couldwell WT. Pituitary carcinoma: a review of the literature. Neurosurg. 2004; Focus 16: E7.
3. Pernicone PJ, Scheithauer BW. Invasive pituitary adenoma and pituitary carcinoma. Major Prob Pathol. 1993; 27: 121-36.
4. Pichard C, Gerber S, Laloi M, Kujas M, Clemenceau S, Ponvert D, et al. Pituitary carcinoma: report of an exceptional case and review of the literature. J Endocrinol Invest. 2002; 25: 65-72.
5. Kaltsas GA, Grossman AB. Malignant pituitary tumors. Pituitary. 1998; 1: 69-81.
6. Scheithauer BW, Kurtkaya-Yapicier O, Kovacs KT, Young WF, Lloyd RV. Pituitary carcinoma: a clinicopathological review. Neurosurgery. 2005; 56: 1066-73.
7. Lehman NL, Horoupian DS, Harsh GR 4th. Synchronous subarachnoid drop metastases from a pituitary adenoma with multiple recurrences: case report. J Neurosurg. 2003; 98: 1120-3.
8. Kumar K, Macaulay RJB, Kelly Michael, Pirlot T. Absent p53: absent p53 immunohistochemical staining in a pituitary carcinoma. Can J Neuro Sci. 2001; 28: 174-8.
9. Thapar K, Kovacs K, Scheithauer BW, Stefaneanu L, Horvath E, Pernicone PJ. Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. Neurosurgery. 1996; 38: 99-107.
10. McCutcheon IE, Pieper DR, Fuller GN, Benjamin RS, Friend KE, Gagel RF. Pituitary carcinoma containing gonadotropins: treatment by radical excision and cytotoxic chemotherapy: case report. Neurosurgery. 2000; 46: 1233-40.

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