



Case Report

Bromocriptine-responsive suprasellar germinoma with the expression of dopamine receptors: A case report

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ABSTRACT

Background: Germinomas are sensitive to radiotherapy and chemotherapy. However, there has been no report involving in the potential therapeutic effect of dopamine agonists (DAs) such as bromocriptine on germinomas.

Case description: A 20-year-old female was presented with bitemporal visual disturbance and amenorrhea. Magnetic resonance imaging demonstrated a huge sellar tumor with upward extension and invasion of the parasellar region. The blood tests showed an exceedingly high level of prolactin. A sellar tumor with hyperprolactinemia was diagnosed, and bromocriptine was initially given. After three months, the tumor volume had been obviously decreased by 82%. However, the tumor re-grew after ten months and the endoscopic endonasal surgery was performed. Histopathological and immunohistochemical examination indicated the patient had a pure sellar germinoma. The tumor cells strongly expressed dopamine 2 receptor and dopamine 5 receptor, which located in the membrane and cytoplasm.

Conclusions: The transient but significant partial responsiveness of germinoma to bromocriptine treatment in this patient is a novel discovery, suggesting that DAs may be a potential therapeutic choice for tumors with the expression of dopamine 2/5 receptors.

1. Introduction

Dopamine agonists (DAs), such as bromocriptine and cabergoline, are the first-line treatment of prolactinomas. DAs are effective in suppressing prolactin (PRL) hypersecretion, reducing tumor size, and restoring gonadal function. The mechanism is believed to involve the dopamine receptor (DR) expression of the tumor cell; a decrease in DR expression has been shown to be associated with the resistance of tumor cells to DAs [1]. However, there is no report for malignant germinomas responsive to DAs treatment. Thus we report here for the first time a pure germinoma responsive to bromocriptine treatment.

2. Case report

In August 2014, a 20-year-old female was admitted into the Department of Endocrinology, the First Affiliated Hospital of China Medical University, with the complaint of amenorrhea for four years

and bitemporal visual disturbance for three years. The blood tests showed an exceedingly high level of PRL (2082.0 mIU/L), whereas levels of other pituitary hormones were within normal range. Magnetic resonance imaging (MRI) demonstrated a huge sellar tumor of 3.3 × 3.3 × 2.3 cm with upward extension and invasion of the parasellar region (Fig. 1A and B). A sellar tumor with hyperprolactinemia was diagnosed, and bromocriptine was initially given (1.25 mg/day). The tumor had decreased progressively in size upon the treatment (at one month: 3.0 × 2.6 × 1.9 cm, 41% decrease; at three months: 1.8 × 2.1 × 1.2 cm, 82% decrease) (Fig. 1C–F). Meanwhile, the serum PRL level significantly lowered to 61.3 mIU/L. Consistently, visual disturbance was alleviated. The patient changed the dosage of bromocriptine into 0.625 mg daily without doctor's permission from February 2015. During this period, she denied any exposure to radiation, including computer tomography examination. Likewise, she did not take any other medications (including corticosteroids) immediately prior to or during the bromocriptine administration.

Abbreviations: DAs, dopamine agonists; PRL, prolactin; DR, dopamine receptor; D2R, dopamine 2 receptor; D5R, dopamine 5 receptor; MRI, magnetic resonance imaging; VIM, vimentin; SALL4, sal-like protein 4; hGH, human growth hormone; PLAP, placental alkaline phosphatase; SY, synaptophysin

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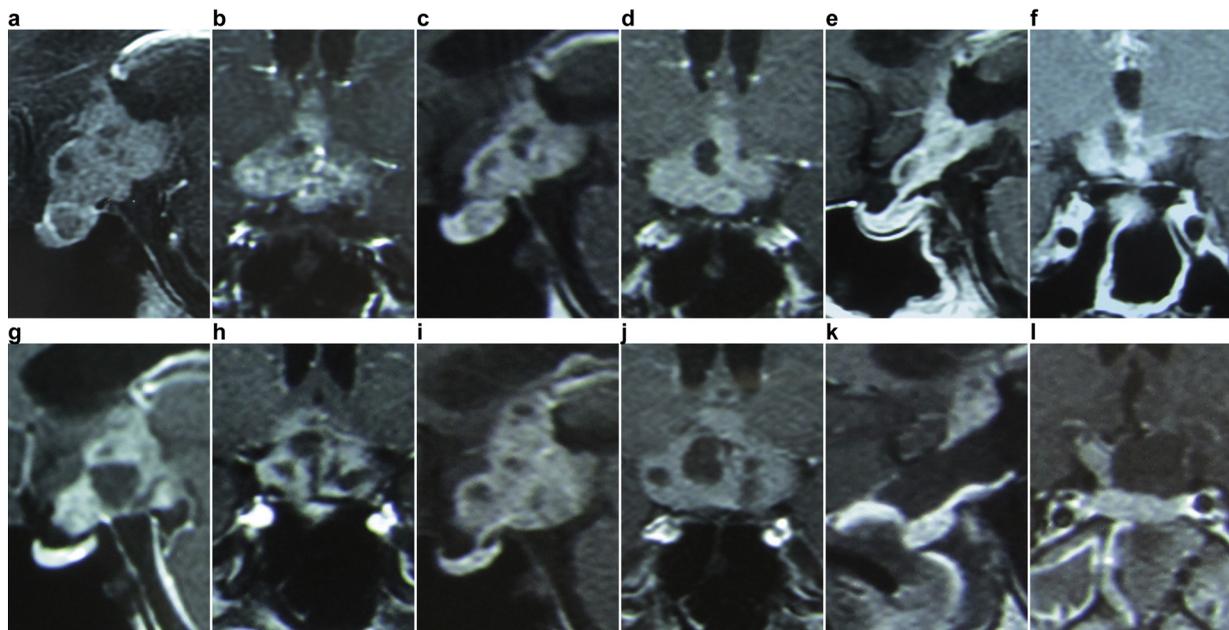


Fig. 1. MR images during the clinical course. A and B, Pituitary MRI before the treatment with bromocriptine. C and D, Tumor shrinkage was confirmed on MR images after 1-month treatment with bromocriptine. E and F, Further tumor shrinkage was confirmed on MR images after 3-month treatment with bromocriptine. G and H, Re-growth of tumor despite bromocriptine treatment. I and J, Tumor size rapidly increased in four months later. K and L, MRI demonstrated the residual tumor after endoscopic endonasal approach surgery.

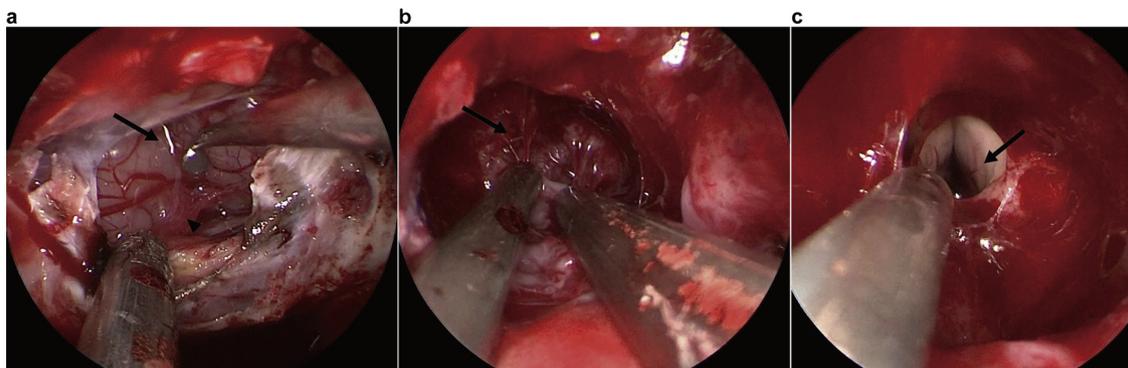


Fig. 2. Intraoperative view of tumor and sellar region. A, Opening the suprasellar arachnoid, the pituitary stalk (arrowhead) and tumor (arrow) were visualized. B, Dissecting and removing the tumor (arrow). C, Direct visualization of the third ventricle (arrow) after removing the tumor.

In June 2015, she was admitted to our department again because of right-sided visual loss. At this time, MRI showed regrowth of the tumor with suprasellar extension ($2.7 \times 2.4 \times 1.5$ cm, Fig. 1G and H). The serum PRL level was 283.0 mIU/L. The dosage of bromocriptine was proposed up to 1.25 mg/d. Four months later, she complained of rapidly deteriorating vision and the ensuing MRI examination revealed increased tumor size ($3.4 \times 3.2 \times 2.4$ cm, Fig. 1I and J). On perimetry testing, the left eye was nearly anoptic (perception of light), whereas the right eye was total blindness. Therefore, the endoscopic endonasal approach surgery was performed. During surgery, an elastic and hemorrhagic tumor with rich vascularization was discovered and pituitary stalk was identified (Fig. 2A). Subtotal resection of the tumor was achieved due to the intense hemorrhage (Fig. 2B and C; Fig. 1K and L). Examining medical history in detail at this moment, the patient reported being polyuria for four years (urine volume: 3000 ml daily). The postoperative recovery was uneventful. However, there was no improvement in her visual disturbance due to the irreversible damage of visual nerves.

Histopathological examination revealed the typical appearance of a germinoma with a two-cell pattern (Fig. 3A). Characteristic large polygonal tumor cells with well-defined cell borders, clear and

abundant cytoplasm and centric nuclei with one or more prominent nucleoli were admixed with small lymphocytes along fibrovascular septa. Foci of hemorrhage and necrosis were also noted. Immunohistochemical studies showed positive results for vimentin (VIM) (Fig. 3B), sal-like protein 4 (SALL4) (Fig. 3C), CD117 (Fig. 3D). In addition, human growth hormone (hGH), placental alkaline phosphatase (PLAP), and synaptophysin (SY) also were positive staining (Supplementary Fig. 1A, B, and C, respectively). PRL staining was negative (Supplementary Fig. 1D). Based on these pathological findings, a diagnosis of a pure germinoma was confirmed.

Considering the initial responsiveness to bromocriptine treatment, we investigated the expression of dopamine 2 receptor (D2R) and dopamine 5 receptor (D5R), which are considered as sensitive biomarkers of tumor cells to DAs treatment, in this germinoma. Interestingly, the tumor cells strongly express these two receptors (Fig. 3E and F), both in the membrane and cytoplasm of tumor cells.

3. Discussion

Intracranial germinomas are rare, with a prevalence of between 0.4 and 3.4% of all primary intracranial tumors, which commonly occur in

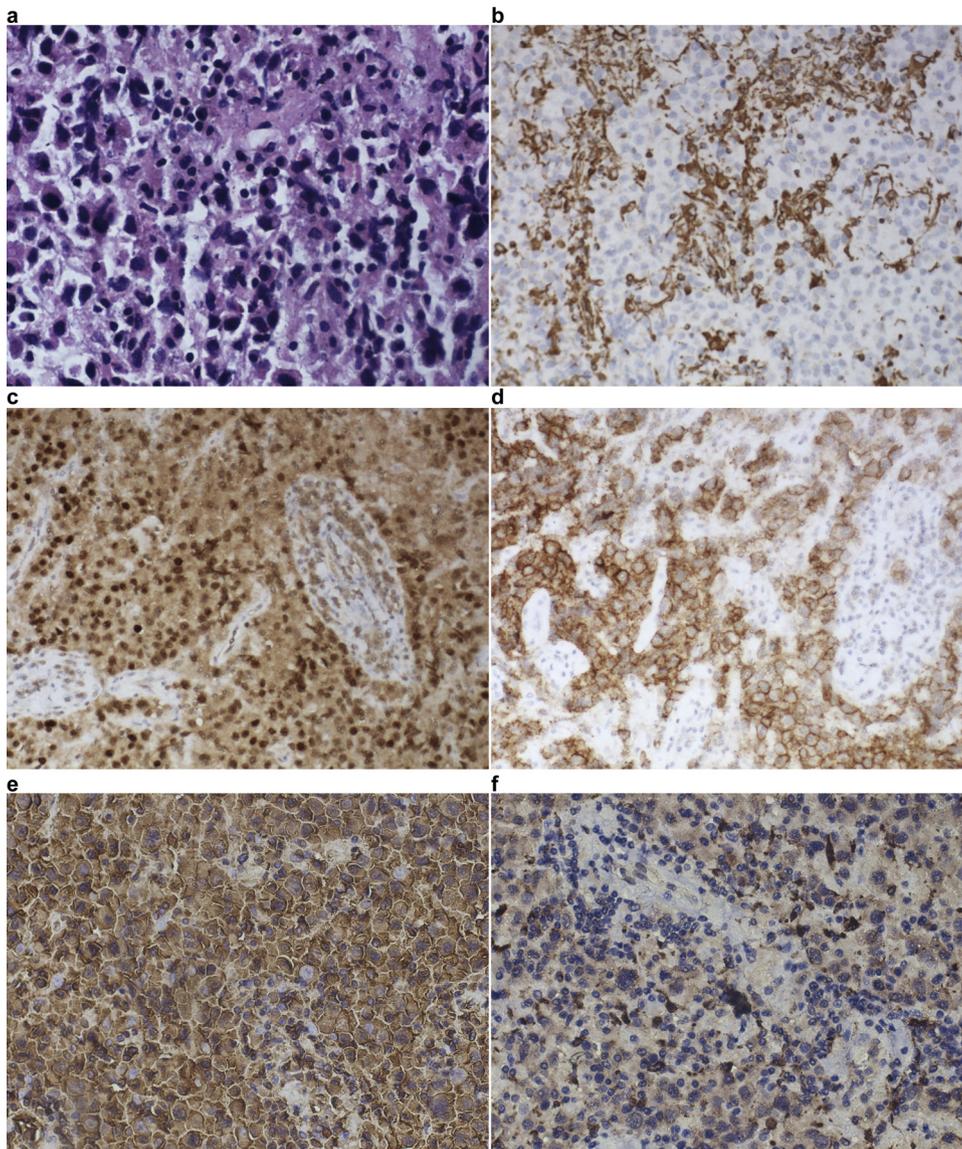


Fig. 3. Immunohistochemistry of tumor cells. A, large and round neoplastic cells with lymphocytic infiltration ($\times 400$). B–D, Positive immunostaining of Vimentin, SALL4, and CD177 ($\times 200$). E and F, strong positive immunostaining for D5R and D2R ($\times 400$).

the pineal gland, posterior third ventricle and suprasellar regions. Following surgery, radiation therapy is commonly used to treat germinoma. However, there are some complications of radiation therapy, such as hypopituitarism, neuropathy, and even radiation-induced brain tumor. In an effort to spare individuals the effects of cranial irradiation, multiagent chemotherapy has now become the potential alternative choice of care for these tumors.

Previously, there were a few isolated cases concerning significant regression of intracranial germinoma after corticosteroids administration. As germinoma was characterized by prominent lymphocyte infiltration, corticosteroids have great lymphocytotoxic effect on lymphocytes. The excellent clinical and the significant radiological response of germinoma to corticosteroids, increases the likelihood that the corticosteroids become the formal clinical treatment of germinoma.

DAs are the first choice for prolactinomas. It is widely considered that DA's curative effect is positively correlated with D2R; that is, tumor cells with relatively higher D2R expression are sensitive to DAs treatment. In contrast, tumor cells with lower or no D2R expression, like some nonfunctional and other types of pituitary adenomas, are traditionally considered to be resistant to DAs treatment. However, it has been reported that D5R also can be activated by DAs like

bromocriptine. Activation of D5R can inhibit the tumor growth through autophagic cell death [1]. This case has clearly showed that a germinoma is responsive to bromocriptine because of the high expression level of DRs.

Previously, Yoshida et al. has been reported that bromocriptine treatment significantly inhibited uterine endometrial adenocarcinoma development with regard to both incidence and multiplicity in rats [2]. Sheikhpour et al. showed that bromocriptine is responsible for induction of apoptosis in human lung cancer cells with normal expression of D2R and can be used in treatment of these tumor cells [3]. In addition, synergistic effect of DAs with other chemotherapeutic agents has been shown to inhibit the growth of other malignant tumors. Frontini et al. reported that the chemoneuroendocrine therapy of weekly low-dose Taxotere plus Cabergoline is a new, effective and well-tolerated therapy for metastatic breast cancer [4]. And, Ding et al. found that bromocriptine with tumor necrosis factor-alpha could reverse hepatocellular carcinoma multidrug resistance (MDR) in nude mouse MDR model of hepatocellular carcinoma [5]. In this case, we first found that a germinoma was responsive to bromocriptine due to strong expression of D2R and D5R in tumor cells. Unfortunately, this tumor was not totally cured and eventually recurred, which might be due to the

heterogeneity of malignant tumor cells and inadequate dose of bromocriptine treatment.

This case report, by showing the responsiveness of germinoma expressed DRs (D2R or D5R) to DAs (bromocriptine), would suggest a possible use of DAs in the treatment of malignant tumors. Therefore, the use of DAs at the time of pathological diagnosis of germinomas, expressed DRs (D2R and D5R), may be administered as part of formal clinical use or as followed standard use by reduced dose and volume irradiation. Furthermore, depending on dopamine receptor expression, stratified personal treatment strategy using DAs could be suggested not only to pituitary adenomas but also other, including malignant tumors.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: <https://doi.org/10.1016/j.clineuro.2018.11.006>.

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