Rapid enlargement of an intracranial germ cell tumor after gonadotropin hormone therapy

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ARTICLE INFO

Article history:
Received 19 August 2015
Accepted 17 January 2016

Keywords:
Gonadotropin hormone therapy
Growth
Intracranial germ cell tumor

ABSTRACT

We report a case of an intracranial germ cell tumor (iGCT) that showed rapid enlargement after human chorionic gonadotropin (hCG) hormone therapy for pituitary hypogonadism. A 16-year-old boy presented with headache and was diagnosed with a suprasellar tumor. He was initially observed without surgery. Intranasal desmopressin therapy was started for central diabetes insipidus, but there was no change in the tumor size on MRI. The diagnosis of the tumor remained unknown for 4 years. Levels of serum gonadotropin hormones (follicle–stimulating and luteinizing hormone) and testosterone progressively decreased, and the patient developed pituitary hypogonadism and complained about his undeveloped beard, lack of underarm hair, and erectile dysfunction. Intramuscular gonadotropin injection (hCG 5000 U × 2/week) was started at age 20. Eight months after the first gonadotropin injection, the MRI showed tumor growth with vivid enhancement. Craniotomy was performed and the tumor was partially resected. The histological diagnosis was immature teratoma. After surgery, the patient was treated with 5 cycles of chemotherapy with carboplatin and etoposide. He also received radiation therapy of 50 Gy (20 Gy tumor bed and 30 Gy whole ventricles) to the residual tumor, after which the tumor decreased in size. We postulate that iGCT may be at risk of progression during hCG hormone therapy. Thus, careful monitoring is required for a patient with iGCT who receives this therapy.

1. Introduction

Human chorionic gonadotropin (hCG) hormone therapy has become the treatment of choice for delayed puberty or infertility [1]. We report a patient in which an intracranial germ cell tumor (iGCT) showed rapid enlargement after hCG hormone therapy.

2. Case report

A 16-year-old boy presented with a headache. MRI revealed an enhanced tumor in the suprasellar region (Fig. 1). The basal serum level of pituitary hormone was within the normal range. Serum and cerebrospinal fluid levels of beta-hCG and alpha-fetoprotein (AFP) were also within normal ranges. Headache improved after admission, and the patient and his parents chose observation. One year later, the patient developed central diabetes insipidus. An initial biopsy was performed via a transsphenoidal approach. The sample contained fibrous tissues without tumor cells. Three years after the first examination, a second biopsy via the ventricle was performed using a neuroendoscope. The sample again contained no tumor cells.

The patient had a thin beard and few underarm hairs at age 20, and he also complained of erectile dysfunction. Luteinizing hormone, follicle–stimulating hormone and testosterone hormone levels were low. Intramuscular gonadotropin injections (hCG 5000 U × 2/week) were started (Fig. 2). Eight months after the first hCG injection, MRI showed tumor growth with partial vivid enhancement. MRI just before surgery demonstrated significant enlargement of the tumor. Bifrontal craniotomy via an interhemispheric trans–lamina terminalis approach was performed. Histological examination of the surgical specimen revealed tubular components lined with a pseudostratified columnar epithelium (Fig. 3a). In the stromal contents between the tubular components, immature cells with oval or distorted nuclei were found (Fig. 3b). The tubular components were immunoreactive for cytokeratin (Fig. 3c). These cells showed moderate mitotic activity (Fig. 3d) and were immunoreactive for vimentin and smooth muscle actin (Fig. 3e, f), and negative for AFP, c-kit receptor-tyrosine kinase, beta-hCG and Oct 3/4 (Fig. 3g–j). A germinoma appearance, with a two-cell pattern of uniform cells resembling primitive germ cells and perivascular lymphocytic infiltration, was not observed. The histological diagnosis was immature teratoma.

The patient was treated with 5 cycles of chemotherapy with carboplatin and etoposide. He also received radiation therapy of 50 Gy. The tumor decreased in size on MRI. There has been no evidence of regrowth in approximately two years of follow-up.

3. Discussion

Gonadotropin hormone therapy with recombinant hCG is well tolerated and effective for stimulation of testicular development in infertile men [1]. However, there are also concerns among clinicians regarding gonadotropin replacement therapy, because of the potential for onset or progression of prostate or breast cancer [2].

The peak incidence of iGCT is in the early teens [3], which is around the onset of puberty triggered by serum pituitary gonadotropin elevation. Jinguji et al. reported rapid growth of an iGCT in a 14-year-old boy after a rise in pituitary gonadotropin

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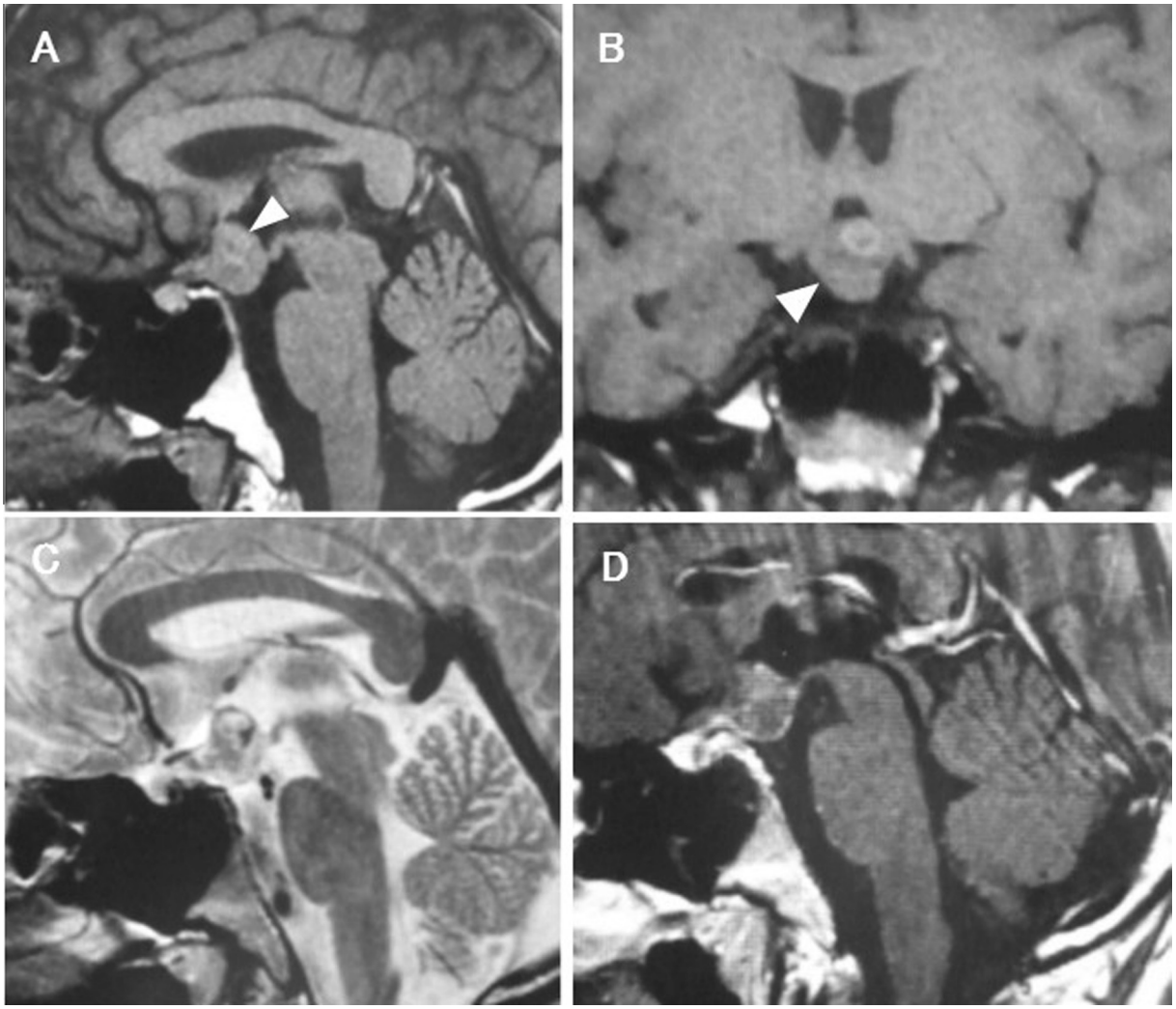

Fig. 1. (a, b; sagittal, coronal) Initial T1-weighted MRI in 2006 revealed a tumor in the suprasellar region (arrowhead), (c) Sagittal T2-weighted MRI showing a mixed intensity lesion, (d) on sagittal T1-weighted contrast enhanced MRI the tumor slightly enhanced with gadolinium.

secretion [4]. The boy presented with gonadotropin-independent precocious puberty at 7 years of age. A small pineal cystic lesion found on MRI might have been a beta hCG producing tumor, but it was unclear whether this mass was an iGCT. After 7 years essentially without tumor growth, the tumor suddenly showed rapid enlargement. A histopathological investigation revealed a mixed GCT with a germinoma and an immature teratoma. The pituitary gonadotropin levels had remained low during the period with no tumor growth, but elevated before the rapid enlargement of the tumor. Thus, rising levels of serum pituitary gonadotropin are considered to be a trigger for growth of iGCTs [3]. Patients with Klinefelter syndrome, a common sex chromosome disorder characterized by hypergonadotropic hypogonadism, may also have an increased risk of development of malignancies. Intracranial GCT may be the most common brain tumor associated with Klinefelter syndrome and this syndrome may be associated with an increased risk of other extragonadal GCTs [5]. However, a larger study by Swerdlow et al. showed that the overall incidence of cancer was not elevated in this cohort [6].

4. Conclusion

The marked tumor growth after hCG hormone therapy suggests that sex–related hormones may affect iGCT. Thus, a patient with iGCT who receives hCG hormone therapy should be closely monitored during treatment.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.