Clinical Case Reports

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CASE REPORT

Long-term remission in an aggressive Crooke cell adenoma of the pituitary , 18 months after discontinuation of treatment with temozolomide

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Funding Information
No funding information provided.

Received: 23 September 2013; Revised: 13 October 2013; Accepted: 23 October 2013

Clinical Case Reports **2014; 2(1): 1–3**

doi: 10.1002/ccr3.39

Key Clinical Message

The clinical course of our patient, who sustained remission status for at least 18 months highlights the chance of long-term hormonal and tumor remission and demonstrates the efficacy and safety of discontinuation of temozolomide therapy. Prospective studies are required in order to define predictors of long-term remission of this promising therapeutic modality.

Keywords

Crook's cell adenoma, Cushing's disease, temozolamide.

Temozolomide (TMZ) is an alkylating imidazole tetrazine derivative, which inhibits DNA replication and triggers tumor cell death. TMZ offers a new perspective in the therapeutic algorithm of aggressive pituitary tumors [1, 2]. However, many areas of uncertainty persist, such as the optimal therapeutic protocol and the disease-free survival after TMZ discontinuation. Here we present a case of an aggressive corticotroph Crooke's cell adenoma (CCA), refractory to multiple conventional treatments with an excellent response to 11 cycles of TMZ, with significant tumor shrinkage, reversal of cranial nerve palsy, and control of adrenocorticotroph hormone (ACTH) hypersecretion, sustained up to latest follow-up, 18 months post-TMZ treatment.

A 55-year-old woman was referred to our clinic in June 2003 with Cushing's disease (ACTH 48.3 pmol/L, urinary free cortisol [UFC] 1119.5 nmol/24 h and cortisol post 2-day dexamethasone suppression 419.3 nmol/L). Magnetic resonance imaging (MRI) showed a 13 × 22 mm mass with suprasellar extension, left cavernous sinus invasion, and encasement of left internal carotid artery. Transsphenoidal surgery was performed, and a CCA, composed of Crooke cells with typical cytoplasmatic structures (hyaline ring of densely arranged microfilaments, large lysosomes, secretory granules around the lysosomes, and at the cell periphery) and, with low cell proliferative activity (Ki67~1%) was revealed. Due to disease persistence (postoperative cortisol 828 nmol/L and ACTH 38.7 pmol/L) treatment with metyrapone and ketoconazole was initiated. MRI examination 3 months postoperatively, disclosed a small tumor remnant encasing the left internal carotid artery and the patient underwent conventional radiotherapy (45 Gy). Three years post radiotherapy ACTH levels were alarmingly raising (812.9 pmo/L) (Table 1) and Gamma Knife (γ-knife) stereotactic radiosurgery (21 Gy, in a single dose) was performed. Left oculomotor palsy developed 4 months post-γ-knife. This treatment failed to control Cushing's disease and 3 years later, MRI demonstrated tumor regrowth (30 × 30 mm), which had spread into both cavernous sinuses with encasement of left internal carotid artery and extended to the suprasellar region (Fig. 1A) with further increase in ACTH levels (1854 pmol/L). Due to the size of the tumor, bilateral adrenalectomy was not an option for the patient.

TMZ was initiated in November 2010. We adopted the standard schedule of TMZ treatment, widely used for

malignant glioma, at a dose of 150–200 mg/m^2 once daily for days 1–5 of a 28-day cycle. The patient also received ketoconazole plus metyrapone and hydrocortisone in a block and a replace regime to control severe hypercortisolism. Three months after treatment initiation, plasma ACTH fell to 135.5 pmol/L. After six cycles of TMZ, ACTH levels further lowered at 31.9 pmol/L, associated with a remarkable regression of the pituitary mass on MRI examination (Fig. 1B). Significant improvement of skin pigmentation and ophthalmoplegia was noted. After 10 cycles of TMZ, the patient developed severe weakness and her body weight had decreased by 11 kg (from 55 to 44). ACTH levels were 21.1 pmol/L, UFC values were 44.1 nmol/24 h and the mean cortisol levels of a 5-point day curve, 15 days after discontinuation of all medications (including hydrocortisone), were 193.2 nmol/L. MRI disclosed a 1.3 × 1.3 cm cystic remnant encasing the left internal carotid artery. At latest follow-up, 18 months after termination of TMZ treatment, the patient remained in remission and she needed hydrocortisone replacement, while ketoconazole and metyrapone were discontinued after the 10th TMZ cycle on September 2011. The tumor remnant on her last MRI was stable, ACTH was 11.9 nmol/L (Fig. 1C), and the morning serum cortisol before the hydrocortisone administration was 1677 nmol/L. The remaining pituitary function was intact.

Table 1. Hormonal and imaging data under variable treatment modalities.

Date	ACTH (pmol/L)	Mean serum cortisol (nmol/L)	Tumor size (mm)	Treatment
June 2003	48.3	890	13 × 22	
July 2003				TSS
August 2003	38.7	828	9 × 6	
October 2003				Conventional radiotherapy
October 2006	812.9	245	14 × 8	ketoconazole metyrapone
January 2007				Stereotactic radiosurgery
November 2009	1350	200[1]	30 × 30	(γ-knife) ketoconazole metyrapone Hydrocortisone
November 2010	1854	220[1]	30 × 30	TMZ Ketoconazole
January 2011	135.5	162[1]	13 × 13	metyrapone Hydrocortisone
April 2011	31.9	185[1]	13 × 13	
September 2011	21.1	193.2[1]	13 × 13	
March 2013	11.9	167[1]	13 × 13	Hydrocortisone

[1]Serum Cortisol before hydrocortisone administration.

This case illustrates a favorable and long-lasting outcome to TMZ treatment of both hormonal hypersecretion and tumor volume regression leading to amelioration of compression effects. Prospective clinical studies on the efficacy of TMZ treatment in pituitary tumors are lacking and most data are derived from similar case reports. Of clinical importance, once treatment is initiated, response after three cycles of TMZ treatment seems to be a good predictor of TMZ effectiveness [1], as was the case with the patient presented in this report. However, the optimum number of TMZ cycles and predictors of long-term outcome, particularly after treatment discontinuation, remain elusive. In an effort to predict TMZ effectiveness,

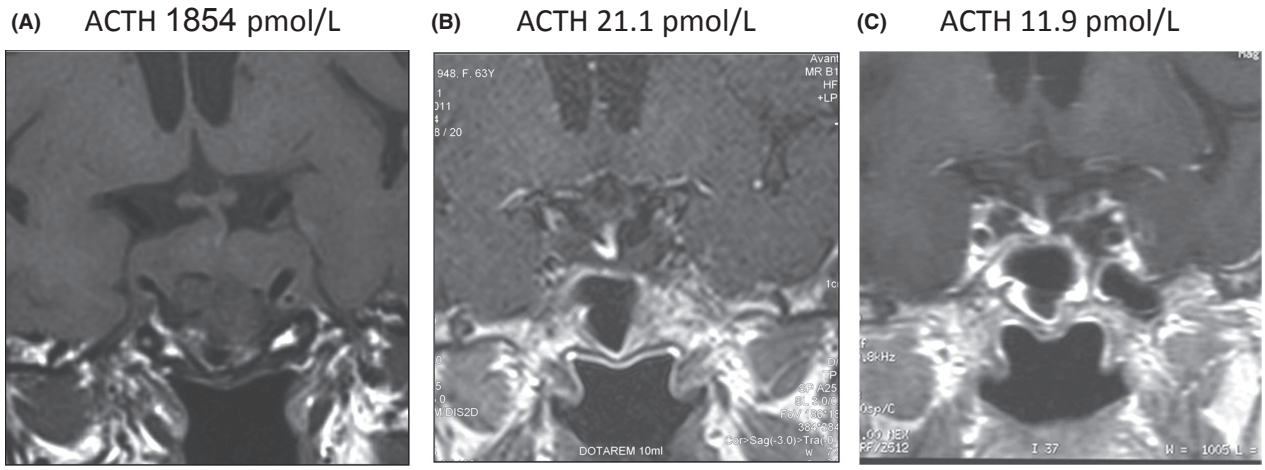

Figure 1. Pituitary MRI before (A), after 10 cycles of TMZ treatment (B) and 18 months after discontinuation of TMZ treatment (C); respective plasma ACTH levels are also noted.

it has been proposed that low tumor expression of *O*6-methyl-guanine-DNA methyltransferase (MGMT), a DNA repair protein that counteracts TMZ antineoplastic action, may predict response to TMZ therapy [2, 3]. Recently, a correlation of the expression of MSH6, a DNA repair protein, with TMZ effectiveness has been proposed, [4] in a limited number of patients. However, availability of immunohistochemical markers has questionable predictive value in routine practice [2]. Note that MGMT immunohistochemistry was not performed in our patient.

With regard to ACTH-producing tumors treated with TMZ, 18 cases were recently reviewed [2]. A reduction in more than 50% in ACTH secretion was observed in 67% patients, while 56% of these demonstrated a reduction in tumor volume of more that 20% after 9.1 ± 4.1 TMZ cycles [2]. CCA is a rare tumor type associated with ACTH hypersecretion. Its clinical course is variable, with many tumors demonstrating, as in our case, an aggressive behavior. Experience of TMZ in this subgroup of pituitary tumors is limited. As reported in the case of two CCA patients, both responded initially to TMZ treatment but one patient exhibited disease recurrence 4 months post TMZ, while the other patient remained in remission [5]. In a recent study, three more patients with CCA were presented [4]; they responded initially, but two of them exhibited tumor recurrence while on treatment for 8 and 9 months, respectively, while the remaining patient showed a complete response and continued TMZ for 20 months. Our study thus represents the first case of a favorable long-term response after TMZ discontinuation in this rare subgroup of aggressive pituitary tumors. In fact, long-term follow-up of responder patients following discontinuation of TMZ has been reported in only few patients. So far, data have been available in only 13 cases with a variety of pituitary tumor types with seven patients considered as stable 6–34 months after cessation [2].

Conflict of Interest

None declared.

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