Early Manifestation of Communicating Hydrocephalus After Fractionated Stereotactic Radiotherapy for Aggressive Giant Atypical Prolactinoma

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Abstract. *Aggressive giant invasive pituitary adenomas refractory to standard surgical or medical treatment remain a genuine challenge. In addition, communicating hydrocephalus (CH) attributed to malabsorption of cerebrospinal fluid (CSF) developing after radiotherapy for pituitary adenomas has not been previously reported. Herein, we describe the case of a 48-year-old male presenting with a giant atypical prolactinoma refractory to previous therapies, including pharmacotherapy and repetitive surgery. He underwent image-guided fractionated stereotactic radiotherapy in 28 fractions, resulting in early manifestation of CH associated with undisputed, both radiological and hormonal response. He recovered well after a shunt placement, with otherwise favorable consequences such as sustained tumor regression, decreasing prolactin level, and retained visual function for a 22-month follow-up. Fractionated stereotactic radiotherapy would provide a viable treatment alternative for these refractory cases, while caution should be exercised regarding the possibility of iatrogenic CH.*

Giant invasive prolactinomas are an unusual subset of macroprolactinomas with a male preponderance (1, 2), and those refractory to standard treatments such as dopaminergic agonists (DA) or surgical debulking have remained genuine therapeutic difficulties (3-6). Furthermore, a subset of them possess a histologically- or clinically-malignant behavior as atypical adenomas or even carcinomas with a predilection for dissemination (7, 8). Radiotherapy has retained a pivotal role for these cases with either primary or disseminated disease as an integral part of the therapeutic armamentarium (9, 10). Concerns about long-term toxicities relevant to antiquated radiation techniques, however, may make practitioners and patients wary of conventionally-fractionated radiotherapy (9). Hence, stereotactic radiosurgery (SRS) has become one of the most preferred and prevailing techniques (9-13), while tumors of >3-4 cm in diameter or juxtaposed to the optic apparatus (OA) lead to substantial compromise in dose prescription for single-session SRS (9, 11, 12).

Giant pituitary tumors, including pituitary adenoma extending into the third ventricle, may cause obstructive hydrocephalus (13). In addition, communicating hydrocephalus (CH) attributed to malabsorption of cerebrospinal fluid (CSF) is a well-described consequence after stereotactic irradiation (STI) for acoustic neuroma (14, 15) and rarely other entities such as meningioma (16). To our knowledge, however, CH developing after radiotherapy including STI for pituitary tumors, including prolactinoma, has not been previously reported.

Herein, we describe a patient harboring symptomatic CH associated with undisputed tumor response which developed early after fractionated stereotactic radiotherapy (FSRT) for aggressive giant atypical prolactinoma, secondary transformation from adenoma, refractory to previous therapies including DA and repetitive surgery.

Case Report

A 37-year-old male initially presented with a giant invasive pituitary tumor over 6 cm in diameter with one-month's history of progressive visual impairment, whose initial clinical diagnosis was non-functioning adenoma. He underwent subtotal removal of the tumor *via* two stages, with subsequent morbidity, including anterior pituitary dysfunction, diabetes insipidus, and worsened visual function. Postoperative examinations revealed an overwhelmingly high prolactin (PRL) level of 22,000 ng/ml and the histopathological diagnosis was consistent with PRL-producing adenoma, suggesting the initial mis-

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Key Words: Prolactinoma, atypical adenoma, giant adenoma, fractionated stereotactic radiotherapy, hydrocephalus.

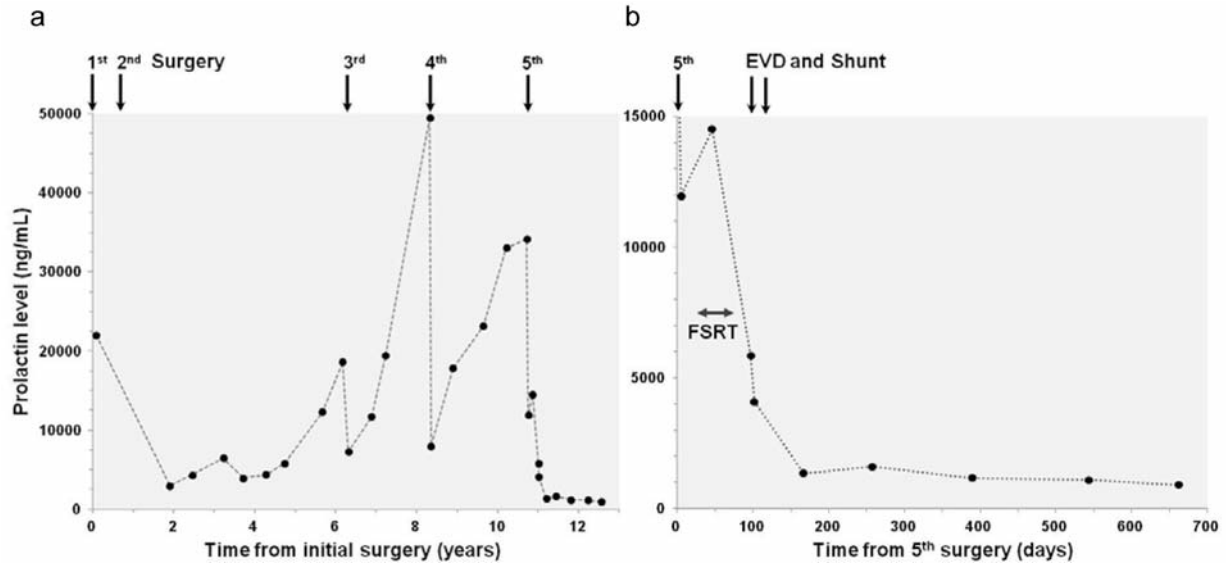

Figure 1. *Transitions of serum prolactin level from the first (a) and the fifth (b) surgical debulking of the tumor.*

Table I. *Dosimetric parameters of initial and boost plans.*

		Initial plan 25 fractions		Boost plan 3 fractions		CD
GTV(cm^3)		87.7		47.7		
PTV(cm^3)		110.7		61.5		
		Dose fr	tDose	Dose fr	tDose	BED2
ICD		2.35	58.75	5.00	15.00	
CTV	D99	1.94	48.50	2.00	6.00	
	D95	2.06	51.75	2.57	7.71	
	D_{mean}	2.28	57.75	2.34	7.02	
	D1	2.44	61.25	5.15	15.45	
PTV	D95	2.01	50.25	2.32	6.96	
Chiasma	D_{mean}	1.94	48.25	0.97	2.91	99.9
	D1	2.05	51.00	1.79	5.37	114.0
ON	D_{mean}	1.05	26.50	0.38	1.14	41.4
	D1	1.91	49.00	1.18	3.54	99.0
Rt. CA	D_{mean}	2.25	54.25	0.92	2.76	123.6
	D1	2.39	58.75	1.85	5.55	141.8
Lt. CA	D_{mean}	2.23	55.75	2.45	7.35	134.3
	D1	2.33	59.00	4.28	12.84	166.4
Brainstem	D_{mean}	1.17	29.50	0.80	2.40	49.7
	D1	2.14	53.50	1.43	4.29	118.1
Mucosa	D_{mean}	1.73	43.75	1.91	5.73	91.9
	D1	2.30	58.25	3.90	11.70	158.1
Lt. parotid	D_{mean}	0.39	9.25	0.55	1.65	13.8

Expressed in units of Gy as otherwise indicated. CD, Cumulative dose; Dose fr, dose per fraction; tDose, total dose; BED2, biological effective dose (α/β=2) calculated according to the linear-quadratic formula: BED=total dose × [1 + (dose per fraction)/n], where n represents the α/β ratio; ICD, isocenter dose; Dn, dose receiving n% of the target volume; D_{mean}, mean dose; ON, optic nerve; CA, carotic artery; Rt., right; Lt., left.

diagnosis due to Hook effect (17). He subsequently received bromocriptine followed by terguride and cabergoline, resulting in a waning response to any DA after the nadir value of 2,970 ng/ml at two years from the onset (Figure 1a), even with cabergoline of 7.0 mg/week combined with terguride of 0.5 mg/day. He underwent additional surgical debulking twice, both resulting in temporal decrease in the PRL value and tumor volume.

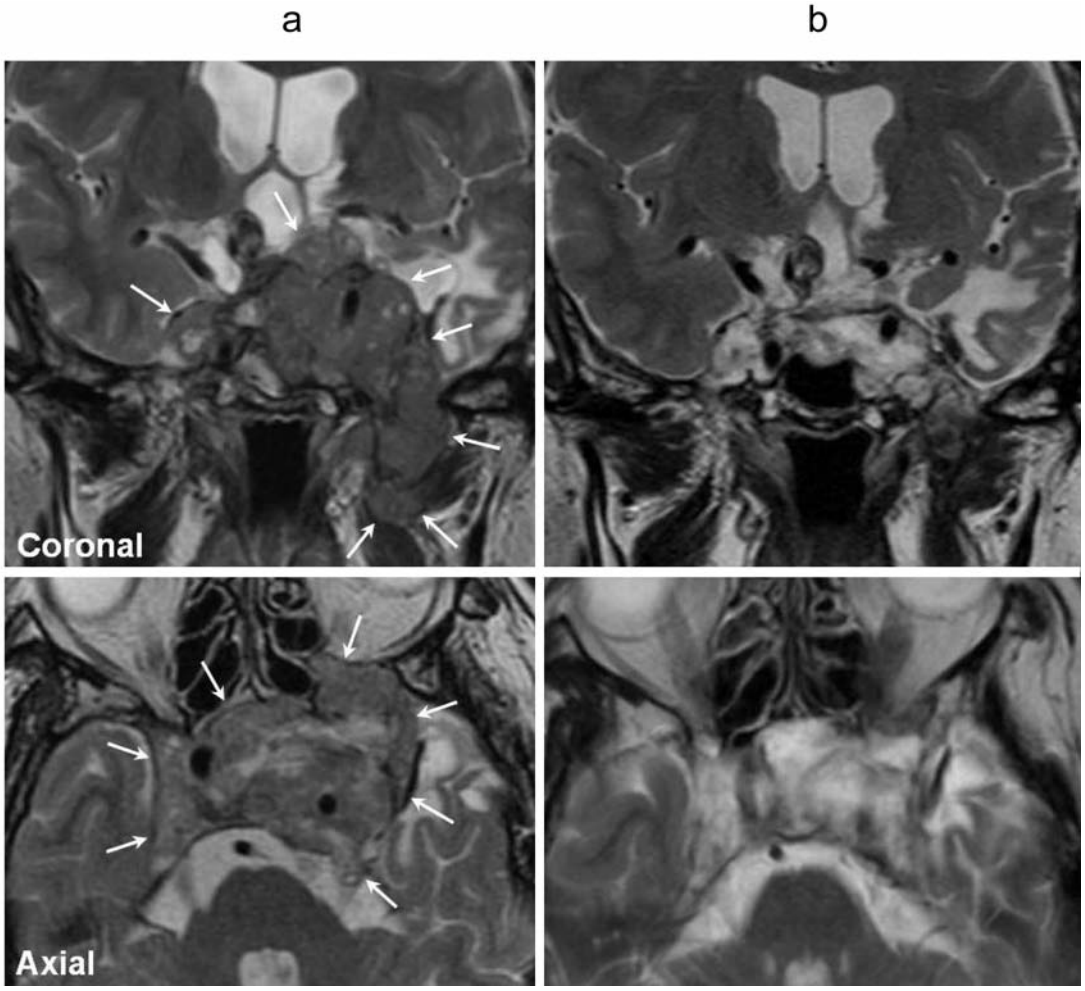

Figure 2. *T2-Weighted images showing undisputed tumor response comparing before (a) and 22 months after (b).*

Despite continued pharmacotherapy, both radiologically and endocrinologically relentless tumor progression was evident at 10.5 years after initial surgery, with a PRL value of 34,160 ng/ml (Figure 1a). At the age of 48, he underwent a fifth surgical debulking of the tumor, resulting in a postoperative PRL level of 11,950 ng/ml. Histological examinations revealed the transformation into atypical adenoma, with an the E3 ubiquitin ligase Mindbomb 1 (MIB1) index of 15% and positive immunoreactivity for p53. The patient was then referred for radiotherapy, whereupon his medical condition was remarkable for panhypopituitarism, left visual loss, left oculomotor palsy, right visual impairment with temporal hemianopsia and decreased acuity, and left trigeminal neuropathy. Radiological examinations revealed that the residual tumor was 87.7 cm^3 in volume, with 7.4 cm in maximum diameter, extending laterally into the bilateral cavernous sinus with encasement of both carotid arteries, caudally into the left parapharyngeal and masticator spaces at the level of oropharynx, and cranially beyond the optic chiasm, and failed to decipher the margination of the optic apparatus (OA) from the tumor (Figure 2).

FSRT in conventional fractionation was, thus, planned to irradiate the remnant tumor in its entirety while preserving visual function. The delivery technique was dynamic conformal arcs in image-guided frameless manner using the Novalis Tx platform (BrainLAB AG, Feldkirchen, Germany and Varian, Palo Alto, CA, USA) equipped with 6D correction system *via* patient immobilization with general masking (18). The gross tumor volume was expanded 1.5 mm isotropically to form the planning target volume (PTV). Treatment planning was based on 5 arcs including 3 non-coplanar arcs under a pencil beam algorithm, constituting the initial plans in 25 fractions followed by the boost in three fractions. For the initial plan, 85% isodose surface was adopted to encompass the PTV boundary to ensure sharper

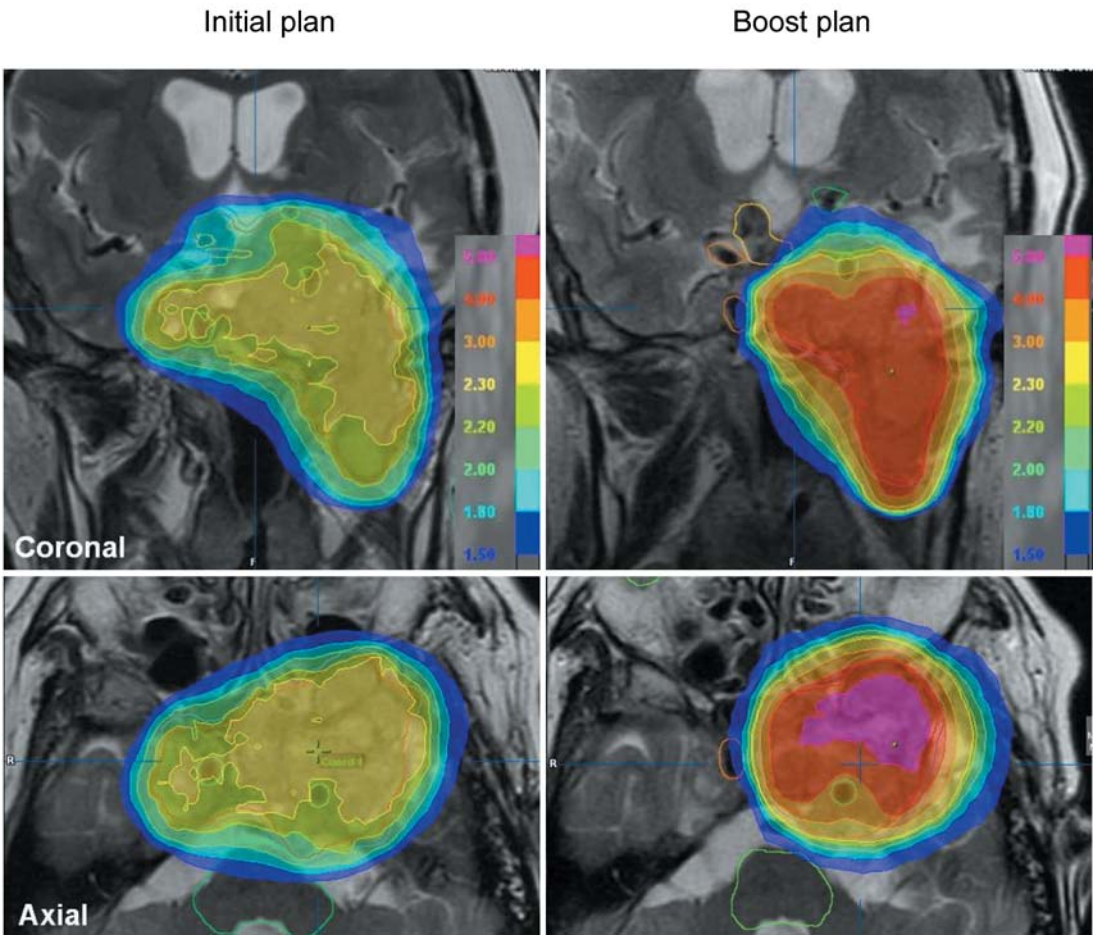

Figure 3. *Representative dose distributions of the initial and boost plans calculated on the X-ray voxel Monte-Carlo algorithm. Isodose surfaces are expediently depicted as absolute doses (Gy) per fraction.*

dose fall-off outside the target (19). To mitigate the dose to the OA and carotid arteries, the plan was optimized *via* manual adjustment of selected leaf positions on beam's eye view (Figure 3) (18). Planning parameters are shown in Table I as the results re-calculated with the X-ray voxel Monte-Carlo algorithm with spatial resolution of 2.3×2.3×2.5 mm^3 and mean variance of 2% inasmuch as this was more accurate for the tumor juxtaposed to the air cavity, with up to 7.6% differences compared to the pencil beam algorithm (20). Transient increase in PRL was noted at 19 days after the initiation of FSRT (Figure 1b). Planned treatment was completed with complaints of fatigue, decreased appetite and low-grade fever at the end of FSRT, which retrospectively were likely, in part, attributable to progression of CH.

He suffered transient loss of consciousness 29 days after the completion (70 days after the initiation) of FSRT and was transferred to our hospital, whereupon radiological examinations disclosed CH with subgaleal fluid collection, along with the controlled tumor of increased signal intensity on T2-weighted image (Figure 4). The patient was urgently placed with an external ventricular drainage, and CSF examinations revealed xanthochromic fluid, with total protein concentration of 596 mg/dl and PRL value of 354.4 ng/ml. Therefore, CSF malabsorption due to early tumor response with protein spillage into CSF was deemed as a major cause of CH. The patient subsequently underwent a ventriculo-peritoneal shunt with subsequent full recovery. At 22 months, he retained pre-FSRT visual function with sustained tumor regression and PRL level decreasing to its lowest value of 906.4 ng/ml during more than 12 years under continuation of DA (Figure 1b and 2).

Discussion

DA has been the first-line treatment for the vast majorities of prolactinomas, even giant invasive adenomas, although a subset of patients exhibit poor response, resistance, or intolerance to DA (2-4, 6). Surgery has solidified its role for

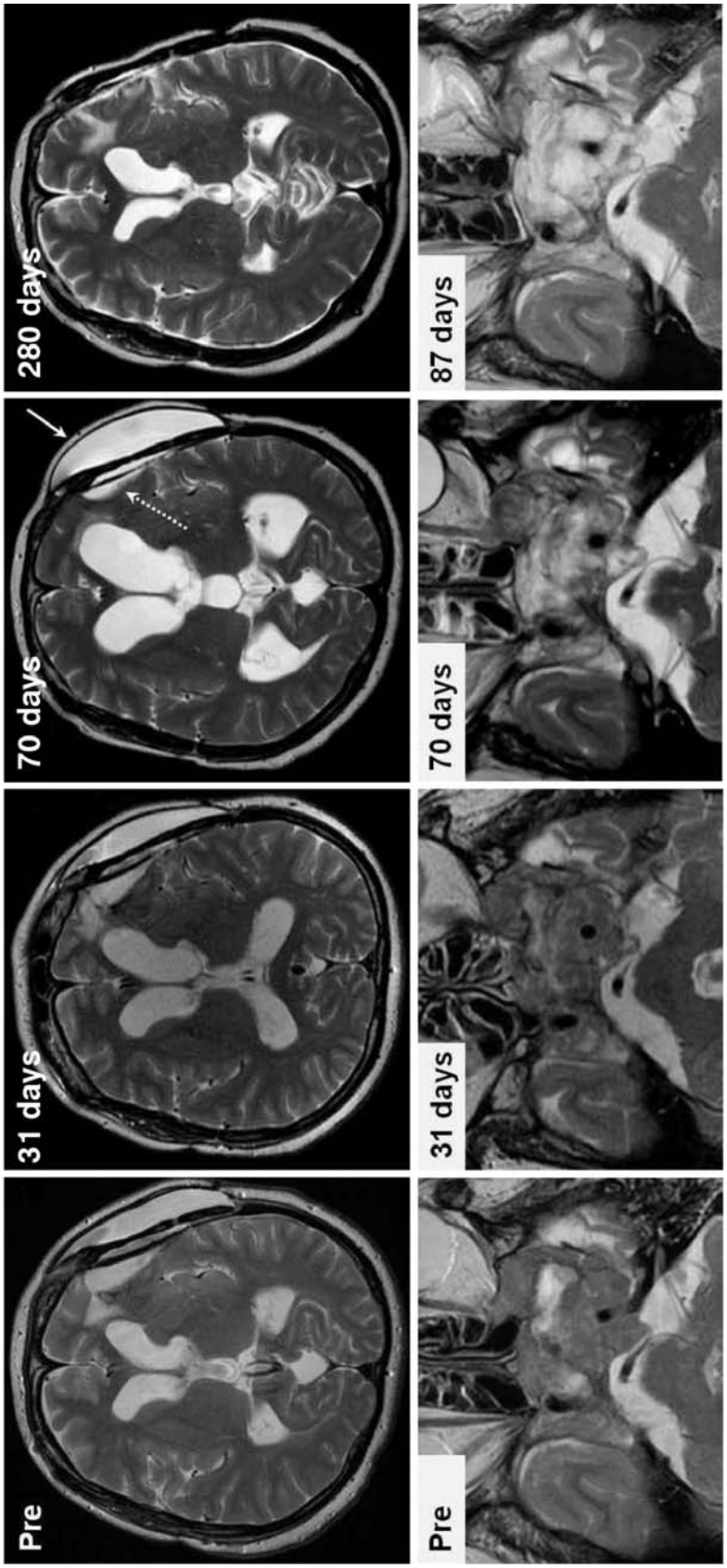

Figure 4. *T2-Weighted images obtained before and 31, 70, 87 and 280 days after the commencement, showing gradual progression of ventricular dilatation, increased subgaleal fluid collection (solid arrow), and decreased subdural hygroma (dashed arrow) for up to 70 days, with subsequent resolution at 280 days (upper panel). Of note are the significant increase in intensity and regression in the size of the tumor for up to 87 days (lower panel).*

managing such cases and is also the *sin-qua-non* for pathological and molecular analyses (1-3, 5, 21). The extent of resection hinges on the tumor volume and the degree of local invasion, with the encasement of carotid artery (Knosp grade 4) rendering the tumor not amenable to total extirpation (5, 9). Radiotherapy is usually reserved for these refractory cases (9). Although single-session SRS or hypo-fractionated SRT of five fractions of fewer is preferred, the efficacy and safety largely depends on the tumor volume, proximity to the OA, and the presence of further extension into the surrounding structures as alluded to above (9, 11, 12). Dose distribution of these STI techniques is intrinsically characterized by inhomogeneous target dose, with sharper increase inside the target boundary, as well as steeper dose falloff outside the target (11, 12, 19). In cases with the OA or carotid artery engulfed by the tumor, these critical structures thus inevitably receive higher doses, analogous to those to the tumor. Furthermore, poor margination of the OA from the tumor can also lead to increased risks of toxicity or jeopardizing of local control (9, 11, 22). Previous repetitive surgery *via* versatile transcranial approaches may also render the patient ineligible for safe and rigid frame fixation for gamma knife use (18).

By virtue of recent advances in image-guidance systems, STI can be implemented even with conventional fractionation in a more accurate and less-invasive fashion (18). We usually consider 50.4-54 Gy in 1.8-2.0 Gy fractions with a homogeneous target dose (90-95% isodose surface for target coverage) for radiation-naïve, large, invasive pituitary adenomas in which the OA is substantially involved in the PTV. The present case represented severe pituitary dysfunction and impaired visual function as the consequences of repetitive surgery and repeated recurrences. These may also render the involved normal structures more vulnerable and susceptible to damage from radiation, whereas the malignant biological behavior may also confer resistance to standard radiation doses. Therefore, we intentionally chose a rather inhomogeneous target dose with conventional fractionation for raising the integral dose to the tumor while mitigating the dose to the normal structures (19), with a subsequent boost to the main tumor-bearing area. As a result, symptomatic CH associated with tumor response unexpectedly occurred within one month after the completion of FSRT. The development of CH in this case was earlier compared to those for acoustic neuromas, in which CH occurs at a median of 11-12 months after STI (14, 15). The early tumor response may be attributed to the atypical histopathological features, with highly proliferative activity and higher radiation dosage to the tumor *via* FSRT. Of note, the PRL level in the CSF was high, and a transient spike in serum PRL was also observed during FSRT. The early tumor response likely led to spillage of the ingredients including PRL of tumor cells into CSF, resulting in CSF malabsorption. Early manifestation and the magnitude of CSF malabsorption may also be relevant to an enormously large tumor burden.

Notwithstanding the short follow-up duration, this case suggested that FSRT provides a promising treatment option for giant atypical prolactinomas refractory to previous therapies. Given the large irradiated volume and higher dose both to the tumor and to the normal tissues, vigilant post-FSRT follow-up is mandatory, with monitoring of the durability of tumor control and potential adverse events, including cranial nerve injuries, brain radionecrosis, vasculopathy, neurocognitive decline, CSF rhinorrhea, and radiation-induced malignant transformation (9, 22). To minimize risks of these untoward effects and to maximize tumor control, early application of FSRT *in lieu* of an attempt at further surgical debulking should be considered, especially in cases deemed not amenable to total resection, when resistance to DA or unrelenting radiological progression is evident, and to circumvent undue risks of repetitive surgery.

Nonetheless, caution should be exercised with regard to the manifestation of CH in cases with large skull base tumors, including giant invasive pituitary adenomas contiguous to the CSF space treated with FSRT. Whole-brain scanning is recommended for imaging surveillance to monitor the whole ventricles. This would also be important to detect any disseminated disease elsewhere in the brain, portending pituitary carcinomas (8, 10).

A subset of aggressive giant invasive prolactinomas refractory to standard treatment still represents a therapeutic challenge (1, 2, 5, 7, 8). Regarding other treatment alternative chemotherapeutic agents, such as temozolomide, have emerged as promising options (23). Whether the combined approach of FSRT with these agents acts synergistically and safely to improve outcomes deserves further investigation.

Nevertheless, the present case suggests that image-guided FSRT is a promising strategy for giant invasive atypical prolactinomas refractory to standard therapies, and also cautions clinicians to the possibility of CH attributed to CSF malabsorption for those contemplating FSRT for such large skull base tumors contiguous to the CSF space. To take full advantage of FSRT, along with obviating untoward sequelae, the early application of FSRT should be considered for these refractory cases before the tumor burden reaches an excessive size and further encroaches on the adjacent structures.

Acknowledgements

This study was supported in part by Grants-in-Aid from the Japanese Society for Promotion of Science (JSPS) KAKENHI (25461911).

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Received January 12, 2014
Revised February 23, 2014
Accepted February 24, 2014