

Chordoid glioma of the third ventricle—a case report and literature review

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Abstract: Chordoid glioma (CG) is a very rare brain tumor. According to the World Health Organization (WHO) classification, it is classified to be a low-grade glioma, class II. It often arose from the third ventricle, along the roof of the ventricle, or the anterior wall of the ventricle. Due to the location of the tumor, the tumor frequently involves the thalamus or hypothalamus region. A 44-year-old man was presented with severe headache, dizziness and unsteady gait for 2 weeks. MRI showed a lesion sized 53 mm × 46 mm in the third ventricle involving right thalamus. Stereotactic brain biopsy was done and diagnosed to be CG. External beam radiotherapy (EBRT) using TomoTherapy[®] was delivered with a dose of 62 Gy in 31 fractions. The tumor responded to the treatment but progressed 5 months after the radiotherapy. The patient died from urosepsis with multi-organ failure 10 months after the radiotherapy. The most common clinical presentation for CG was headache. Neuroradiologically, the tumor was distinct in its location and pattern of intensity in MRI. Histopathologically, the tumor was characteristics with cords or clusters of epithelioid cells resembling chordoma with lymphocyte infiltration. The disease is usually treated by gross total resection (GTR), with promising outcome. For those who are unsuitable for total resection, subtotal resection (STR) or biopsy followed by radiotherapy was performed in some literatures. The role of radiotherapy was not clear in this disease. Literatures regarding this disease and the role of radiotherapy were reviewed and discussed.

Keywords: Chordoid glioma (CG); radiotherapy; tomotherapy; third ventricle; brain tumor

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Introduction

Chordoid glioma (CG) is a low-grade brain tumor originating from the thalamus or anterior wall of the third ventricle. It was classified as grade II glioma according to the WHO since 2000 (1). Less than 100 cases have been reported to the public indicating its rarity so far (2). Zarghouni *et al.* reviewed previous cases reported which concluded that CG affected women more than men at a rate of 2:1 and the age of diagnosis were most likely between 30 and 60 years old (3). To be further, CG is a type of brain tumor which has its unique histologic appearance and specific location (4). Neuroradiologically, the tumor tends to be ovoid in shape and locates in the region of the hypothalamus/anterior third ventricle with uniform enhancement and intensity in magnetic resonance imaging (MRI) scans (5). Histologically, clusters and cords of oval-topolygonal epithelioid tumor cells with abundant eosinophilic cytoplasm are seen as the hallmark of the CG (6). CG is most treated with maximal surgical removal in the literature. If gross total resection (GTR) was not possible due to the location and the size of the tumor, subtotal resection (STR) was often the choice of treatment. After STR, few were submitted to adjuvant radiotherapy. There're controversies regarding the dosage and the technique of radiotherapy for this disease.

Here we present a case of CG over the third ventricle who received external beam radiotherapy after stereotactic brain biopsy. The roles of radiotherapy and other clinical



Figure 1 Brain magnetic resonance imaging (MRI). (A) Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) image (TR/TE/TI: 9,502/135/2,250) reveals an ovoid long T2 lesion arising from right side of 3rd ventricular region, majorly involving right thalamus, and causing obstructive hydrocephalus; (B) contrast-enhanced axial T1-weighted MR image (TR/TE: 400/10) reveals only faint scattered contrast enhancement of the tumor. TR, repetition time; TE, echo time; TI inversion time.

presentations were discussed subsequently in more detail and literatures were reviewed as well.

Brief history

A 44-year-old man presented to our hospital with 2 weeks of severe headache, progressive unsteady gait and dizziness. Mild slurred speech was also found by the family for about a month. There was no sensory or motor function impairment, language function impairment, memory loss, arrhythmia, change in urination frequency, change in bowel habit, or change in visual fields. MRI showed an ovoid long T2 lesion with faint scattered contrast enhancement arising from right side of 3rd ventricular region, measuring 53 mm × 46 mm in diameter, majorly involving right thalamus, and causing obstructive hydrocephalus (Figure 1). Brain tumor was first suspected with increased intra-cranial pressure (IICP). The neurological symptoms of the patient mentioned above, including headache, unsteady gait and dizziness, recovered with controlling the IICP by steroids and glycerol. Only slurred speech continued after the IICP was controlled. The patient's Karnofsky score was 90 and Eastern Cooperative Oncology Group (ECOG) performance score was 1 before any treatment started.

The patient then received a stereotactic brain biopsy. The diagnosis was CG. The tumor revealed epithelioid neoplastic cells with cord-like structures within a myxoidrich stroma. The immunohistochemical (IHC) staining profiles showed positivity for GFAP, S-100 and CD34, negativity for EMA, with a Ki-67 index of 6.1% (*Figure 2*). The surgeon considered the tumor inoperable due to the location of the tumor. Local treatment by radiotherapy was suggested and accepted by the patient and family.

The patient was immobilized with a head rest, custom thermoplastic mask and underwent 3 mm sliced CT scan with contrast enhancement for simulation. The gross tumour volume (GTV) was contoured and a 3 mm margin was added to create planning target volume (PTV). The patient received radiotherapy using Helical TomoTherapy® (Accuray Incorporated, Sunnyvale, CA, USA). TomoTherapy[®] uses a fan-beam delivery system to deliver rotational intensity-modulated radiation therapy. The course of fractionated radiotherapy consisted of 62 Gy/31 fractions given 5 days per week of a period of 7 weeks. The brainstem was limited to less than 55 Gy and optic chiasm, lens, and optic nerves were also contoured with constrains to fulfill current standards for organ at risks. Ninety-eight percent of the PTV was covered by 62 Gy isodose curve line, and total GTV was covered 100% (Figure 3). The dose-volume histogram and dose to the region of interest (ROI) were illustrated in Figure 4. The patient received the radiotherapy uneventfully and the slurred speech recovered after the treatment. The acute side effect of the treatment was mild headache only. No other neurological sequelae

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Figure 2 The immunohistochemical (IHC) staining. The tumor demonstrates cords and clusters of large epithelioid tumor cells embedded in a vacuolated mucin-rich stroma. (A) Positive for GFAP (H and E, 400×); (B) positive for S100 (H and E, 400×); (C) positive for CD34 (H and E, 100×). GFAP, glial fibrillary acidic protein.



Figure 3 Dose distributions of the treatment plan in axial, sagittal and coronal planes. The GTV (green dots), PTV (red dots), and isodose lines of 105% (yellow), 100% (blue), 95% (purple), 90% (mustard), 80% (green), 70% (orange), 50% (sky-blue), 30% (light-yellow), 10% (beige) and 5% (pink) are depicted. GTV, gross tumour volume; PTV, planning target volume; A, anterior; R, right; L, left; P, posterior; GH, gantry head.

developed during or after the treatment. The patient maintained his previous Karnofsky and ECOG scores, 90 and 1, respectively.

MRI which has been done one month after radiotherapy showed decreased tumor size (28.6 mm × 18.5 mm) as compared to prior MRI (53 mm × 46 mm). Focal cystic change with marginal contrast enhancement was noted within the tumor (*Figure 5*). However, tumor regrowth was noted 5 months later in follow-up MRI (*Figure 6*). The regrowth of the tumor was observed from the same location, which was within the GTV field. We considered it a residual tumor with progression. Several episodes of headache and unsteady gait have been noted due to IICP and controlled by medication during the follow-up period. The patient lost to follow-up 6 months after the treatment. The patient developed high fever with urosepsis and visited our emergency department 10 months after the radiotherapy. His condition deteriorated rapidly and expired due to multi-organ failure.

Discussion

Clinical presentation

To begin with, less than 100 cases of CG were reported in the literature with strikingly similar clinical features. The median age at diagnosis was 48 years (7). The female to male ratio was reported to be 2:1 (3). The median tumor diameter was about 3 cm, ranged from 1.5 to 7 cm. The clinical presentation was highly associated with the location





Figure 4 The dose-volume histogram (DVH) for the tumor and the region of interest (ROI). Circles indicate constraints. PTV, planning target volume.



Figure 5 Post-radiotherapy brain magnetic resonance imaging (MRI). (A) Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) image (TR/TE/TI: 6,310/110/2,200) reveals decreased lesion size and decreased obstructive hydrocephalus as compared to prior MRI; (B) contrast-enhanced axial T1-weighted MR image (TR/TE: 400/8) reveals focal cystic change with marginal contrast enhancement of the tumor. TR, repetition time; TE, echo time; TI inversion time.

of the tumor. Most part CG arose from the thalamus or the anterior wall of the third ventricle. Thalamus was believed to act as a relay between the subcortical area and the cerebral cortex. Thalamus possesses an important role for different functions of human body such as cognition, sensory function, motor and language function, memory, consciousness and the circadian rhythm. Tumors which originated from the inferior portion of the anterior third ventricle could bring about endocrine complaints which comprised diabetes insipidus (DI) and hypopituitarism (8). In the review article written by Ampie *et al.*, the most common symptoms presented for CG were headache (40%), visual symptoms (35.8%), and mental status changes (27%) (7). The patients often experienced headache or other neurological symptoms



Figure 6 Brain magnetic resonance imaging (MRI)—regrowth of tumor. (A) Axial T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance (MR) image (TR/TE/TI: 9,502/134/2,250) reveals central long T2 change over right thalamus, right corpus striatum, right corona radiata and right lateral ventricle. Tumor progression was considered; (B) contrast-enhanced axial T1-weighted MR image (TR/TE: 400/10) reveals tumor regrowth with contrast enhancement. TR, repetition time; TE, echo time; TI inversion time.

over a long period of time prior to the diagnosis and its mean time from onset of symptoms to surgical management was 22.1 months (range, 0–20 years) (9).

In our case report, the patient reported to have intermittent headache for years and the clinical presentation included headache, dizziness and unsteady gait. After controlling IICP, only slurred speech was noted before his treatments. The patient has only slurred speech prior to the treatment after controlling the IICP.

Radiological findings

MRI was usually the better mean of imaging examination for tumor which arose from the third ventricle or thalamus. The differential diagnosis for solid tumors from this area included ependymoma, germinoma, brain metastasis and CG. Ependymoma which located in the supratentorial periventricular region generally appeared variably from strong solid enhancing masse to more heterogeneous mass with cystic component. Germinoma arose majorly from pineal region and also along the floor of the third ventricle, appearing with contrast enhancing solid mass. Brain metastasis should always be considered in adult brain mass whenever systemic malignancy was noted. CG usually presented as an ovoid solid mass known as hypo or isointense on T1-weighted MRI imaging with strong homogeneous contrast enhancement (10). Around

10% of the cases, CG might demonstrate heterogenous enhancement on T1 weighted MRI (11). On T2 weighted MRI, CG frequently appeared as hyperintense or isointense lesions (12). The findings of CT for CG typically appeared both circumscribed and hyperdense lesions that enhanced homogenously after contrast administration. However, the findings in the literature were inconsistent. Atypical CT features reported including intratumoral hemorrhage, heterogeneous contrast enhancement, and calcification. To conclude, our case indicated the relatively untypical appearance of CG in his diagnostic MRI as well as CT images. The tumor only showed faint scattered contrast enhancement in T1-weighted magnetic resonance (MR) image. In CT scan, the lesion was hypodense without homogeneous enhancement. Otherwise, the tumor was consistent with the findings in the literature. In T1weighted MR image, the tumor revealed hypodense ovoid lesion. In T2-weighted MR image, it showed a hyperintense lesion.

Histological diagnosis

The characteristic of CG has its unique histologic and IHC features. Histologically, CG would resemble chordomas and chordoid meningiomas in its features of the clusters and cords of epithelioid cells within a mucinous vacuolated stroma (13). The IHC features included the positivity

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for GFAP, EMA, CD34, cytokeratin, S100 and vimentin. Lymphocyte infiltration was also commonly seen. The proliferative activity was generally low for CG. Mitoses were consistently low and no necrosis was ever reported (9,14-16). Desouza et al. have reviewed 50 cases of CG and indicated that the lymphocytic and plasma cell infiltrates were discussed in the ratio of 48 to 50 cases (96%). Likewise, the mucinous or myxoid stroma was discussed in the ratio of 49 to 50 cases. However, significant mitoses have only been found in 1 of the 45 cases so far. Ki-67 was recorded in 22 cases and ranged from 0.3% to 5% (17). Sanches et al. reported a unique case, a 59-year-old woman with a 2 cm CG, demonstrating GFAP and vimentin positivity, EMA negativity, and Ki-67 expression 20% (10). In our case, the tumor revealed epithelioid neoplastic cells with cord like structure in myxoid-rich stroma. The IHC stain showed positivity for GFAP, S-100 and CD34, and negativity for epithelial membrane antigen (EMA). Additionally, the Ki-67 index was 6.1 % and it was slightly higher among other cases reviewed.

Treatments

CG was most generally treated by surgical resection. The surgical approaches included trans-lamina terminalis, transcallosal resection, and transcortical resection. Less than half of the patients (44%) were amenable for GTR due to the location of the tumor. Approximately, 45% of the cases received STR and 10% of them only received biopsy. In addition, complications after GTR, including hypothalamic dysfunction and transient DI, were in the percentage of 22.2 and 16 respectively. GTR remained the most prognostic factor for CG. No tumor recurrences were reported in the GTR group where 1-, 3-, and 5-year progression free survival (PFS) for STR was 85.2%, 71.0%, and 35.5% respectively (P=0.0276) in the literature (7). Moreover, some studies comprised of radiotherapy partly from the treatment for CG. The radiotherapy techniques included stereotactic radiosurgery (SRS), conventional external beam radiotherapy (EBRT), and intra-tumor radiotherapy (ITRT) using Iridium-192 (Ir-192) seed implantation. Above all, SRS was the majority reported in the review of the literatures. Reifenberger et al. reported the first case ever who received gamma-knife radiosurgery (GKRS) after STR for CG in a 56-year-old woman. The patient has been alive for 3.5 years (15). Nakajima et al. proposed that a 49-year-old woman received STR followed by SRS and its report has showed no regrowth of tumor within

2 years. The SRS was delivered by GKRS with marginal dose of 15-18 Gy (18). Chung et al. reported a patient that the recurrence at 8 months following STR and GKRS (marginal dose 20 Gy) required subsequent resection for recurrence (19). Kobayashi et al. indicated that two cases receiving only biopsy followed by GKRS with marginal dose 10.5-11 Gy, and were clear for diseases 70 and 66 months after the radiosurgery, respectively. Another case published from the same group was that a 61-year-old woman underwent STR and GKRS (marginal dose 12 Gy) has been clear for disease for 12 months before incidental death from an accident (20). In addition, the ITRT by using radioactive seed insertion was also reported in the literature. Kurian et al. brought out two cases of CG in their thirties both treated by ITRT with Ir-192. In both cases, one who received STR and Ir-192 implantation has been alive for at least 15 months in the follow-up. However, one who received biopsy following by Ir-192 recurred after 9 months died shortly after the repeat surgery for the recurrent tumor. The detail of the prescription for the Ir-192 treatment was not presented in the original article (21).

Nevertheless, the combination of SRS and conventional EBRT was reported in one case study by Tonami *et al.* They mentioned that a 42-year-old woman with a 1-year history of amenorrhea and memory impairment was given a diagnosis of CG which treated with STR. A total of 52 Gy of EBRT in conjunction with a 20 Gy delivered by SRS was given after the surgery. The patient was clear for tumor recurrence after 9 months follow-up (22).

Moreover, the use of EBRT along with or without STR was sparse in the literature. Brat et al. reported that two cases who received STR followed by EBRT. One 59-year-old man who received STR and EBRT developed recurrence and expired after 3 years. A 31-year-old female received STR and adjuvant EBRT has been alive for 4 years by follow-up (23). Hanbali et al. reported that a 57-year-old man with the history of hypertension, diabetes mellitus and an old myocardial infarction presented with a 1.5 cm oval lesion centered in the lamina terminals region. He received STR followed by EBRT in the University of Texas, MD Anderson Cancer Center. The dosage of EBRT was 54 Gy in 30 fractions. He developed headache, short-term memory loss, and worsening confusion and disorientation 7 months after the EBRT. Image studies revealed tumor progression (2 cm in diameter) which was removed totally. The patient died of a massive myocardial infarction 2 months after the salvage surgery (24). To date, Kobayashi et al. reported the best result for those who received STR or biopsy alone

Nakajima

et al. (18)

Brat

et al. (23)

Chung

et al. (19)

Case

No.

1

2

3

4

5

6

7

8

Table 1 Reported cases of chordoid carcinoma treated with radiotherapy

61/F

49/F

59/M

31/F

48/M

PR

PR

PR

PR

Biopsy

	1				17					
)	First author (reference)	Year of publication	Age/sex	Initial procedure	RT technique	RT dose	Recurrence or progression	Retreatment	Status	Follow-up
	Kurian <i>et al.</i> (21)	2005	32/F	PR	ITRT	NA	_	_	Alive	15 mo
			37/F	Biopsy	ITRT	NA	Yes, 9 mo	PR	Died	11 mo
	Hanbali <i>et al.</i> (24)	2001	57/M	PR	EBRT	54 Gy	Yes, 7 mo	GTR	Died	9 mo
	Tonami <i>et al.</i> (22)	2000	42/F	PR	EBRT; GKRS	EBRT 52 Gy; marginal 20 Gy	-	-	Alive	9 mo
F	Reifenberger <i>et</i> <i>al.</i> (15)	1999	56/M	PR	GKRS	NA	-	-	Alive	42 mo
	Kobayashi <i>et al.</i> (20)	2013	55/F	Biopsy	GKRS	Marginal 11 Gy	-	_	_	_
			31/F	Biopsy	GKRS	Marginal 10.5 Gy	-	_	_	_

Marginal 12 Gy

Marginal 12 Gy

NA

NA

Marginal

18-20 Gy

Yes. NA

Yes. 8 mo

RT, radiotherapy; PR, partial resection; ITRT, intra-tumor radiotherapy; EBRT, external beam radiotherapy; GKRS, gamma-knife radiosurgery; NA, not available; GTR, gross total resection; mo, months; M, male; F, female.

GKRS

GKRS

EBRT

EBRT

GKRS

followed by radiotherapy, since both cases from their study survived for more than 5 years (20). The cases reported in the literatures that include radiotherapy in the treatment were summarized in Table 1 (15,18-24).

2003

1998

2007

In our case, only biopsy was performed before EBRT due to the location of the tumor and to the tight adhesion of the adjacent structure. SRS was not suitable for this case since the maximal diameter of the tumor prior to treatment was 53 mm. Therefore, EBRT was chosen as the treatment technique. The tumor was contoured based on 3 mm CT simulation images with contrast enhancement. A 3 mm margin was added to the GTV to create PTV. The dose to PTV was 62 Gy in 31 fractions. Here we chose a higher prescribed dose with a smaller PTV according to the literature reviewed. The earliest report from Brat et al. showed long term survival for two cases who received partial resection followed by EBRT, but the prescribed dose was not stated clearly (23). In GKRS series, a marginal dose of 10-12 Gy was often used after the biopsy to maintain a local control (20). Another case with a local control of 9 months received a boost of 54 Gy by EBRT after partial resection and GKRS (11 Gy marginally) (22). In another case, tumor

heavily. The pattern of failure demonstrated in our case echoed to the cases reported in the literature. Yet again,

smoothly.

emphasized the importance of possible resection before any type of radiotherapy started. Symptoms of IICP including headache and vomiting have occurred after the tumor regrowth. Ten months after the radiotherapy, the patient died of urosepsis and multi-

organ failure.

Alive

Alive

Alive

GTR

recurrence was observed 7 months after partial resection and adjuvant EBRT of 54 Gy (24). It seemed reasonable for

In general, a 1–2 cm margin is suggested outside of GTV

to form a PTV for low-grade gliomas. Since our patient had

only slurred speech before the radiotherapy, we wanted to

maintain his neurological function as much as possible. To

sum up, instead of treating the patient with 50-55 Gy with

a 1-2 cm margin, we ended up treating him with 62 Gy

with a 3 mm margin. The patient completed the treatment

However, the regrowth of the tumor was observed

5 months after the completion of EBRT. In our case, the

tumor regrows from the same location where it was treated

us that a higher dose was needed for this rare disease.

24 mo

36 mo

48 mo

60 mo

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Conclusions

CG was a rare disease which arose from the thalamus or from the anterior wall of the third ventricle. GTR remained the mainstay of the treatment and should be considered in spite of all possibilities. The role of EBRT in this disease has not been fully known so far. For those cases who only received biopsy, the choice of definitive treatment is crucial yet limited. Our case report demonstrated that biopsy followed by EBRT may not be enough for long term control. To date, GKRS followed by biopsy with a marginal dose of 10–12 Gy may be a better choice than EBRT. If the tumor was not suitable for GKRS, EBRT with adequate dose and margins may be an option. Further investigations were needed to determine better treatment strategies for this disease.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tro.2018.01.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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