Case Report

Supratentorial intraventricular rosette-forming glioneuronal tumors – Case report and review of treatment paradigms

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INTRODUCTION

Rosette-forming glioneuronal tumors (RGNT) are rare, slow growing mixed cell tumors. RGNTs were first described as a distinct entity in 2002 and added to the WHO classification of tumors of the central nervous system in 2007 as a Grade 1 tumor alongside the papillary glioneuronal tumor.[8,9] RGNTs typically occur in young adults between the ages of 25 and 33 and display a preference for the posterior fossa. They can lead to gradually worsening symptoms of headaches, ataxia, and...
vertigo, from both local mass effect and cerebrospinal fluid (CSF) obstruction. In rare cases, distal extension into the pineal gland, optic chiasm, subcortical structures, and supratentorial ventricular system has been observed.

A meta-analysis of cases compiled until December 2012 found that out of 85 RGNTs, 80% (68) of them occurred in the posterior fossa while only 15.3% (13) occurred supratentorially. The remaining reported cases were spinal (1) or occurred in more than one location (3). We identified only six published cases of RGNTs where the tumor either originated in or extended to the lateral ventricular system, of which three tumors were only localized to the lateral ventricles.

Here, we present the unusual case of a histopathologically confirmed RGNT which originated from the lateral ventricle but which also demonstrated infiltrative properties. To the best of our knowledge, this is only the fourth such case in the literature. The unique presentation of this patient and his subsequent hospital course may be useful in guiding future discussions around the management of this rare tumor.

CASE REPORT

A 41-year-old male with no significant medical history presented to an outside hospital with a 10 day history of continuous headaches, initially rated as 2/10 but occasionally rising to 4/10 on the visual analog pain scale. His headaches were localized to the right occipital region and were unresponsive to acetaminophen and ibuprofen. He had some mild gait difficulty but no nausea or emesis. A computed tomography (CT) scan identified a mixed density 6.0 cm intraventricular mass with dilatation of the left lateral ventricle and a 1.4 cm rightward bowing of the intraventricular septum.

He was started on dexamethasone and referred to our hospital for further workup. He underwent a preoperative magnetic resonance imaging (MRI) of the brain, with and without gadolinium, which showed a heterogeneously enhancing lesion with a cystic component. The lesion was emanating from the roof of the left lateral ventricle from the region of the corpus callosum.

On neurological examination, there were no significant deficits.

It was decided to surgically resect the lesion. The primary goal of the surgery was to debulk the majority of the lesion and restore CSF flow pathways. Therefore, we chose to approach the lesion along its long axis through the left frontal horn of the ventricle. The patient was counseled preoperatively that a second staged parieto-occipital approach might be necessary to remove the remainder of the lesion, depending on the pathology and the extent of resection during the initial surgery. A bifrontal craniotomy with the left interhemispheric transcalsalal approach was performed for resection of the tumor. The interhemispheric approach was chosen over the transcortical trans-ventricular approach because of the extension of the tumor into bilateral
lateral ventricles. The interhemispheric approach, being a midline approach, gave us access to bilateral ventricles without significant brain retraction and without traversing the cerebral cortex. An endoscopic portal approach was not used considering the size and extension of the tumor into the lateral ventricles. While the endoscopic approach might have been well suited for a biopsy of the lesion, it is not optimal for debulking and dissection of large lesions.

Intraoperatively, using a left interhemispheric approach, a small (<1.5 cm) corpus callosotomy was performed to enter the left frontal horn of the lateral ventricle where the tumor was debulked using bipolar cautery, suction, as well as a cavitron ultrasonic aspirator (CUSA). Within the left lateral ventricle, there was large cyst that was exerting mass effect on the septum pellucidum and displacing it into the right lateral ventricle. The cyst was drained. The solid portion of the tumor was emanating from the lateral wall and roof of the left ventricle, from the region of the posterior corpus callosum. The CUSA was used debulk the solid portion of the tumor. On debulking of the tumor, the ventricle walls collapsed inward and further resection was carried out cautiously because of tumor invasion into the ependymal walls of the left lateral ventricle. The deep venous drainage of the brain was embedded within the caudal aspect of the tumor extending into the third ventricle. These vessels were carefully preserved. On conclusion of the resection, an external ventricular drain (EVD) was left behind in the left lateral ventricle. The EVD was weaned and removed a couple of days after surgery. Immediate postoperative noncontrast CT and T1 with contrast MRI showed sub-total resection (STR) of tumor with resolution of mass effect and no postoperative hydrocephalus [Figure 3a and b].

The patient was ultimately discharged home within a week and toward the end of his stay, was ambulating freely without any complaints and possessed an intact neurological exam as assessed by the discharge physician. He was seen in clinic at 3- and 6-months follow-up postsurgery. He had complete resolution of his headaches and remained neurologically intact without any deficits. His 6-month postoperative MRI showed stable lesion with minimal enhancement, markedly decreased from prior [Figure 3c]. Long-term care plan called for MRI surveillance and possibly repeat surgery in the event of tumor progression.

Pathology showed a solid-appearing, glioneuronal neoplasm composed of monotonous cells with round nuclei, punctate chromatin, and cytoplasmic clearing in a neuropil-like background. The tumor cells were arranged in vague neurocytic rosettes and loose perivascular pseudorosettes in a lightly myxoid background. Vessels within the tumor were seen to be thickly hyalinized and there were focal piloid areas with eosinophilic granular bodies and Rosenthal fibers [Figures 4-6]. Active mitoses were difficult to find, although there was microvascular proliferation with slightly
As described earlier, although RGNTs predominantly affect young adults with a mean age range of 24.8–33 years, although cases as young as 12 and as old as 70 have been reported.\(^8,9,14,18,29,30\) Females also appear to be twice as likely to be affected as males.\(^{19,22}\) In our case, our patient was a 41-year-old male which is somewhat outside of the typical age and gender predominance. Due to the RGNT’s low mitotic and proliferative activity, most clinical effects develop over a prolonged period of time and display mass effect type symptoms that are location dependent.\(^1\) Given this patient’s tumor location in the left lateral ventricle, it was able to grow to 6 cm before being detected, which may explain the advanced age on presentation.

Occasionally, the patients can present acutely due to complications associated with tumor growth, as in a 20-year-old patient who developed emergent symptoms of obstructive hydrocephalus secondary to intratumoral hemorrhage after the RGNT likely necrosed on outgrowing its vascular supply.\(^{11}\) As described earlier, although RGNTs originate more frequently in the posterior fossa, more distal points of origin have also been identified. In our literature review using PubMed (Keywords: Rosette Glioneuronal tumor + lateral ventricle), we found only six cases where an RGNT involved the lateral ventricular system [Table 1].\(^{2,7,24,27,29}\) Three patients had tumors that were limited to the lateral ventricles. Interestingly, one of these patients had a history of neurofibromatosis-1, as well as a history of chemotherapy for a typical juvenile pilocytic astrocytoma in the hypothalamus 7 years prior. However, the association between that and his RGNT was unclear.\(^{27}\)

**DISCUSSION**

In this report, we detail the disease course and treatment of a 41-year-old patient who presented with an infiltrative RGNT of the left lateral ventricle. To the best of our knowledge, this is only the fourth case in literature, where the tumor was restricted to the lateral ventricles.

As the name implies, RGNTs are characterized by the presence of glial and neurocytic cells with a neuronal rosette and/or perivascular pseudorosette component and a glial component.\(^9\) This suggests that these tumors may derive from a common precursor cell.\(^{21}\) The subependymal plate, a cell layer that is similar in structure to the periventricular germinal cell matrix of infants, which is a source for both gliogenesis and neurogenesis is thought to be this point of origin.\(^{8,10,17,20}\) Their predilection for the fourth ventricle and surrounding posterior fossa structures may be explained by the embryological course of neurodevelopment although the exact mechanism is still unclear.

**Clinical presentation**

RGNTs predominantly affect young adults with a mean age range of 24.8–33 years, although cases as young as 12 and as old as 70 have been reported.\(^{8,9,14,18,29,30}\) Females also appear to be twice as likely to be affected as males.\(^{19,22}\) In our case, the embryological course of neurodevelopment although the exact mechanism is still unclear.

**Treatment and follow-up**

Similar to other symptomatic low grade gliomas, RGNTs can be suitable candidates for surgical resection and the vast majority of patients (>90%) undergo either gross-total resection (GTR) or STR resection, and can remain progression-free for up to 30.2 months.\(^{12,23,30}\) Biopsy is another option that has been used in situations where the surgeon felt resection was unnecessary or was too risky.\(^{23}\) Yang et al.’s 2017 review of 141 RGNT cases found that GTR was performed in 48.9%, incomplete resection (STR and partial) in 37.5%, while biopsy was performed in 13.5% of patients. Only 1.4% of patients underwent chemotherapy, and 4.3% underwent radiotherapy (RT). STR progression-free survival (PFS) was found to be comparable to GTR (hazard ratio [HR] 0.655, 95% confidence interval [CI] 0.028–15.569, \(P = 0.793\)), while the mixed group of biopsy and partial resection was found to be associated with higher rates of tumor progression compared to GTR (HR 98.258, 95% CI 1.339–7211.531, \(P = 0.036\)) and partial resection was found to be associated with higher rates of tumor progression compared to GTR (HR 98.258, 95% CI 1.339–7211.531, \(P = 0.036\)) respectively. They also showed that progression was less likely in adult patients than in pediatric patients (HR 0.003, 95% CI 0.000–0.181, \(P = 0.005\)) and that the risk of progression was higher in solid RGNTs that in ones with cystic components (HR 78.739, 95% CI 1.479–4192.776, \(P = 0.031\)).\(^{129}\)
| Study       | Patients (n) | Age | Gender | Symptoms                                      | Location                                                                 | Modality: Radiographic features                                                                 | Treatment                          | Follow-up time (months)/ outcome | Notes                                                                 |
|-------------|--------------|-----|--------|-----------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------------------|---------------------------------|
| Wang 2009   | 1            | 16  | F      | Seizure w/ LOC 1 month prior                  | third, fourth ventricles, aqueduct, bilateral lateral ventricles          | MRI: Heterogeneous enhancement (T1C), hypointensity (T1), isointensity (T2), diffuse intensity (FLAIR) CT: Isodense; MRI: heterogeneous enhancement, hypo/iso intense (T1), hyper/hypo intense (T2), iso/hyper intense (FLAIR) | Ventrulostomy and Biopsy (R lateral ventricle) | 7/No recurrence                 | 46 Gy RT 1 month after surgery; VP shunt 5 months after surgery |
| Xiong 2012  | 1            | 38  | M      | Visual disturbances for 1 month               | Septum pellucidum, third and bilateral ventricles                       |                                                                                                                  | STR (R frontal craniotomy)         | 6/No recurrence                 | -                               |
| Kemp 2012   | 1            | 33  | M      | Incidental on MRI follow up                  | Frontal horn of L lateral ventricle                                      | MRI: Enhancement in L lateral ventricle (T1C)                                                                    | GTR (Intraventricular transcallosal approach) | -                           | History of NF-1; received RT and CT 7 years prior to surgery Postoperative RT 54 Gy to tumor mass, 50 Gy to whole ventricular volume |
| Allinson 2015 | 1            | 33  | F      | Headaches, Blurry vision, nausea, intermittent dizziness | Fourth ventricle with extension to third and lateral ventricles          | MRI: Hydrocephalus, multifocal nodules, heterogeneous enhancement (T1C)                                           | Ventrulostomy and Biopsy (third ventricle) | -                           | -                               |
| Yang 2017   | 2            | -   | -      | -                                             | Lateral ventricles                                                      | Pt 1 - CT: Calcification; MRI: heterogeneous enhancement (MRI), facilitated diffusion (DWI), hypointensity (T1), hyperintensity (T2) Pt 2 – MRI: hypointensity (T1), hyperintensity (T2), heterogeneous enhancement, facilitated diffusion (DWI) | -                                   | -                           | -                               |
| Current case | 1            | 41  | M      | Headaches                                     | Lateral ventricles, extending into third ventricle                      | CT: Heterogeneous enhancement, Isodense, Hydrocephalus; MRI: Hydrocephalus, Heterogeneous enhancement; Hypointensity anteriorly | STR (Intraventricular Transcallosal approach) | 6/No recurrence                 | -                               |

RT: Radiotherapy, Gy: Grey, Pt: Patient, STR: Subtotal resection, CT: Chemotherapy, VP: Ventriculoperitoneal, NF: Neurofibromatosis, GTR: Gross total resection
Interestingly, even though these tumors are assigned as WHO Grade I, infiltration of surrounding structures and ventricular infiltration is frequently observed and can lead to rather high complication rates (>45%) on resection.\textsuperscript{[1,2,4,30]} While the report does not make it clear how many of the STR patients had adjuvant therapy in the form of chemotherapy (CT) or RT, the authors note that four patients received RT, three of whom remained stable; and two received combined radiochemotherapy, only one of whom remained stable.\textsuperscript{[29]} Postoperatively, adjuvant chemotherapy can be considered to prevent tumor progression, control aggressive variants or in situations where resection is difficult or incomplete, although overall it is rarely administered.\textsuperscript{[5,12,16]}

Schlaman\textit{e}t al. performed an earlier literature review in 2014 which cites three STR patients receiving a median of 55 Gy through focal RT but did not provide their specific PFS and overall survival (OS). For the 52 patients in this particular paper of a pooled cohort with outcome data, PFS and OS rates at 2 years were both 100%. The favorable prognosis of RGNTs is also reflected by the low overall rates of progression and death at long-term follow-up, which was 11.6% and 4.7%, respectively, with a mean follow-up of 28.5 months.\textsuperscript{[16,30]} However, given the low mitotic activity and WHO I status of these lesions, a longer time interval follow-up may be more meaningful.

Within the five cases of the lateral ventricle cohort with reported data, only 60% (3/5) underwent surgery for resection [Table 1]. Biopsy was done in 2/5 (40%) patients who subsequently received RT.\textsuperscript{[1,24]} One author felt that resection was not feasible given the extension throughout the ventricular system.\textsuperscript{[21]} Both patients recovered uneventfully after surgery although one received a ventriculoperitoneal shunt 5 months after surgery [Table 1]. In our case, since the tumor was also blocking CSF outflow, surgical resection was preferred so that the patient could avoid having a shunt placed, which about 20% of patients require.\textsuperscript{[30]} Given the localized nature of this patient’s cystic tumor, we opted to forego adjuvant therapy and placed the patient under surveillance with the option to reoperate in the case of recurrence.

Pathology and molecular profile

The characteristic histological profile of neurocytic rosettes and perivascular pseudorosettes in a glial setting was observed in our patient. This was confirmed by the positive stains for GFAP, S-100, OLI2, and SOX10 in the glial component, with synaptophysin staining neurocytic rosettes and perivascular structures. Interestingly, while EMA was found to be absent in a large systematic review of 57 RGNT cases, EMA was weakly positive in our patient.\textsuperscript{[19]} This antigen has been associated with identification of ependymomas however its significance here is unclear.\textsuperscript{[6]} Another marker, D2-40, which is a marker against an oncofetal antigen and lymphatic endothelium, was also found to also be weakly positive for our patient.\textsuperscript{[13]} After an exhaustive literature search, we were unable to find any other report of a D2-40 positive or EMA positive RGNT, although the significance here is still unclear.

CONCLUSION

Given the uneventful and sustained neurological recovery of our patient, we demonstrate that STR continues to be a safe and effective treatment option for RGNTs. Further research into the risk factors that predispose these tumors to originate outside of the posterior fossa in uncharacteristic locations may be warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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