Case Report

High-Grade Intraventricular Astroblastoma in a Young Adult: A Rare and Controversial Tumor to Manage

Abstract
Astroblastoma is a rare primary central nervous system tumor of controversial site of origin. They account for 0.45%–2.8% of all primary neuroepithelial central nervous system. It has been reported in paediatric age group with bimodal age distribution affecting more females with male to female ratio being 1:11. Astroblastomas are controversial and challenging tumors in terms of diagnosis and therapeutics. Since it carries an unpredictable disease course it needs a regular follow up even for low grade tumor. Authors have tried various schedules of post op radiotherapy after maximum safe resection. Various chemotherapeutic drugs combination have also been tried without much success. We here report a 35 years old female patient who was diagnosed with high grade astroblastoma referred for post-operative radiotherapy after gross total resection. Since it is extremely rare tumor, its treatment still not well defined and also makes it difficult conduct studies to examine tumor characteristics.

Keywords: Adjuvant radiotherapy, astroblastoma, brain tumor, intraventricular tumor

Introduction
Astroblastoma is an extremely rare and challenging neuroepithelial primary tumor of uncertain origin. It accounts for 0.45%–2.8% of all neuroglial tumors, and it is mainly located in the cerebral hemispheres, mainly occupying frontoparietal hemisphere, although other locations such as brainstem, cerebellum, hypothalamus, and intraventricular have also been documented.[4] Astroblastoma shows a bimodal age incidence with cases being reported in young adults as well as older patients. It was initially described by Bailey and Cushing in 1926 as a separate glial tumor and further characterized by Bailey and Bucy in 1930. Controversies exist regarding its cellular origin; it shares features of both astrocytomas and ependymomas.[5] It has been listed among “other neuroepithelial tumors” in the WHO classification of tumors of the central nervous system. The most recent revision describes astroblastoma as a high-grade (Grade 4) neuroepithelial tumor of unknown origin.[1] They generally present with symptoms suggestive of raised intracranial tension, focal neurological deficits, and epileptic episodes. This tumor is prone to misdiagnosis as it shares radiologic and histopathologic features with other glial tumors. The standard of care treatment is not well defined and hence represents a challenging tumor in terms of diagnosis, classification, and further treatment. Maximum safe resection is the treatment of choice as like for other primary brain malignancies. For high-grade lesions, adjuvant radiotherapy can be added for local control. Oncologists have tried cyclophosphamide-, cisplatin-, and etoposide-based regimens for these tumors. Treatment with vascular endothelial growth factor inhibitors in the form of bevacizumab has also been attempted without much success. Hence, the role of chemotherapy for this tumor is still not clear.[4] Here, we present a case of high-grade astroblastoma in a 35-year-old female referred to us for postoperative adjuvant radiation therapy.

Case Report
A 35-year-old female presented to the outpatient department with the chief complaints of severe headache, recurrent episodes of projectile vomiting, and generalized weakness for 15 days. The patient had evidence of weak gag and...
swallowing. She also had an absent cough, and the patient was not able to expel out the excessive secretions, hence she underwent tracheostomy and started on nasogastric tube feeding.

She was clinically evaluated and advised to undergo magnetic resonance imaging (MRI) brain [Figures 1, 2 and 3] which revealed altered signal intensity lesion of size approximately 3.5 cm × 3.0 cm × 4.5 cm in the midline posterior fossa in relation to the fourth ventricle/vermis anteriorly indenting over the inferior part of the pons and cervicomedullary region with resultant mild proximal dilatation of the supratentorial ventricular system. Lesion was isointense to mildly hyperintense on fluid-attenuated inversion recovery diffusion-weighted imaging (FLAIR) and T2 images. It was isointense to slightly hypointense on T1W1 images. Inferiorly the lesion was extending till cervicomedullary region with concern raised for neoplastic etiology.

The patient underwent a midline suboccipital craniotomy and tumor decompression with placement of ventriculoperitoneal shunt within 15 days of presentation.

Cerebrospinal fluid culture was also done with no growth. Postoperative histopathology [Figures 4, 5 and 6] revealed tumor cells arranged in perivascular pseudorosettes with short and eosinophilic cytoplasmic processes extending toward vessel wall. Vascular hyalinization and perivascular sclerosis were also noted. Individual tumor cells were round, oval to epithelioid, pleomorphic, hyperchromatic with high N:C ratio, coarse chromatin, and eosinophilic cytoplasm. Mitotic figures noted 2/10 hpf. Area of fibrillarity, hemorrhage calcification, and congested hyalinized vessels were noted. On immunohistochemistry, tumor cells were positive for glial fibrillary acidic protein (GFAP). The histopathological features were suggestive of high-grade astroblastoma.

Postoperative noncontrast computed tomography brain showed postoperative changes with extra-axial subdural pneumocephalus along the vermis and bilateral cerebellar convexity with mass effect in the form of compression of the vermis and bilateral cerebellum, brainstem, and fourth
ventricle with draining shunt extending from the fourth and third ventricles with mass effect in the form of compression of the fourth ventricle and cisternal effacement.

The postoperative patient was referred to the radiation oncology department for radiotherapy. We had planned for 60 Gy in 30 fractions for a period of 6 weeks at 2 Gy per fraction.

**Discussion**

Astroblastoma is an extremely rare and uncommon glial tumor encountered in routine clinical practice. It is predominantly observed in cerebral hemispheres (significantly in the frontal lobe, parietal lobe, and temporal lobe) of young adults but also affects other sites such as brainstem, cerebellum, optic nerve, cauda equina, and hypothalamus. It accounts for approximately 0.45%–2.8% of all neurological tumors. It can occur at any age and has been reported during childhood period (5–10 years) and in young adults (21–30 years). Females being diagnosed more with male-to-female ratio reported to be 1:11. The mechanism of tumorogenesis is still not well defined. It is a unique tumor and shares features of both astrocytoma and ependymoma. Since Bailey and Bucy reported the condition for the first time in 1930, this tumor has been reported sporadically in the literature. Astroblastoma is associated with variable outcomes and is a highly debatable entity. Brain tanyctyes are believed to the source of origin of these tumors. Tanyctyes are involved in neuropeptide transport. Tanyctyes have resemblance with some rare brain tumors such as subependymoma and astroblastoma. These tumors are sometimes referred to as tanyctytomas.

Histologically, spindle-shaped cells with short, broad tapering processes are arranged in a perivascular pattern forming pseudo rosettes, reminiscent of ependymomas. These tumors stain positive for vimentin and S-100, which are more characteristic of astrocytic origin.

Astroblastomas are also GFAP, epithelial membrane antigen, cytokeratin, and Olig2 positive and negative for isocitrate dehydrogenase (IDH) and TP53 mutations. Differentiation into low grade and high grade is based on the features such as mitotic rate and degree of cellular atypia and necrosis. There is existence of two distinct zones. The first zone comprises cells around blood vessels with extensive sclerosis (astroblastoma pseudo rosettes). These cells are GFAP and S-100 positive and demonstrate a low Ki-67 index. The second zone is highly cellular with distinctly fewer rosettes and contains noncohesive cells depicting a more rhabdoid appearance. This is positive for S-100 and negative for GFAP and has a higher Ki-67 index. The second zone confers a higher grade to the diagnosis.

Brat et al. have demonstrated some data on its molecular genetics of astroblastoma. They exhibit chromosomal aberrations in the form of gain of chromosomes 19 and 20. Other alterations such as losses on 9q, 10 and X chromosome have also been observed. Shuangshoti found loss of heterozygosity at the D19S412 locus on 19q in a cerebral astroblastoma. More recently, an absence of IDH½ and TP53 mutations, which are known to be involved in the development of low-grade gliomas, was shown in astroblastoma.

Imaging finding can offer help in the diagnosis and prognosis. Astroblastomas often demonstrate T1 and T2 prolongation relative to white matter, with well-circumscribed boundaries and heterogeneous contrast enhancement. The enhancement characteristics can set it apart from meningiomas, which tend to exhibit a homogenous enhancement. Their characteristic supratentorial location also helps set them apart from ependymomas which usually involve the posterior fossa. Calcifications are consistent imaging finding and would be unusual for glioblastoma multiformes (GBMs) and Atypical teratoid and rhabdoid tumors (ATRTs).


| Reference                  | Gender male/female | Age  | Symptoms                  | Radiology/location | Surgery | Radiotherapy | Chemotherapy | Grade |
|----------------------------|--------------------|------|---------------------------|--------------------|---------|--------------|--------------|-------|
| de Reuck et al., 1975[19]  | 1                  | 61   | Cognitive disturbance     | Solid/frontal      | -       | -            | -            | Low   |
| Husain and Leestma, 1986[20]| 1                  | 3    | Seizures, hemiparesis     | Solid/frontal      | -       | -            | Vincristine  | Low   |
| Bonnin and Rubinstein, 1989[21]| 10/13              | 5-58 | Seizures, Hemiparesis     | Solid cystic/17 lobar | 2 pineal | 12 total     | 11 patients  | 13 low |
|                            |                    | mean21.2|                      | 1 suprasellar      | 1                     | 11 subtotal   | 5 patients   | 8 high |
|                            |                    |       |                           | 1 subcortical      |                      |              |              | 2 intermediate |
|                            |                    |       |                           | 1 cerebellar       |                      |              |              |       |
|                            |                    |       |                           | 1 fourth ventricle |                      |              |              |       |
|                            |                    |       |                           |                     |                      |              |              |       |
| Pizer et al., 1995[14]     | 1                  | 17 days| Irritability              | Solid cystic/frontal | Subtotal | Vincristine  | Etoposide | Low   |
| Thiessen et al., 1998[22]  | 1/6                | 1.2-51| Headache                  | 3 frontal          | 4 total   | 3 patients   | 5940 cGy    | 3 low  |
|                            |                    | Mean12.67|                      | 3 parietal          | 3 subtotal |              |              | 4 high |
| Brat et al., 2000[12]      | 4/16               | 3-46 | Seizures, Hemiparesis     | Solid cystic/9 frontal | 7 parietal | 18 total     | 10 patients  | 10 LG  |
|                            |                    | mean14|                      | 2 temporal          | 2 subtotal |              | 38 Gy-72 Gy | 10 HG  |
|                            |                    |       |                           | 1 occipital         |                      |              | Mean 52.5   |       |
|                            |                    |       |                           | 1 midbrain          |                      |              |              |       |
| Port et al., 2002[21]      | 1/5                | 3-46 | Headache                  | Solid cystic/3 frontal | 1 temporal | 5 total     | 3 patients   | 3 LG   |
|                            |                    | mean20.5|                      | 1 parieto-occipital | 1 subtotal |              | 5400 cGy    | 3 HG   |
|                            |                    |       | Motor deficit             | 1 corpus callosum   |                      |              |              |       |
|                            |                    |       |                           | Frontal             |                      |              |              |       |
|                            |                    |       |                           | Total               |                      |              |              |       |
| Sugita et al., 2002[23]    | 1                  | 33   | Seizures                  |                           |                      |              |              | LG    |
| Catalán-Uribarrena et al., 2002[24] | 1  | 17 | Headache                  | Solid cystic/frontal | Total |              |              | LG    |
| Kim et al., 2004[25]       | 1                  | 7    | Headache                  | Solid/brainstem     | Total |              | Yes          | LG    |
| Kim et al., 2004[26]       | 1                  | 15   | Headache                  | Solid cystic/frontal | Total |              | 4500 cGy    | HG    |
| Caroli et al., 2004[27]    | 1                  | 30   | Headache                  | Solid/temporal      | Total |              | Yes          | HG    |
| Navarro et al., 2005[28]   | 3/5                | 1.8-14.5| Headache                  | 4 solid             | 6 total   | 6 patients   | 5 patients   | 4 LG   |
|                            |                    | mean7|                      | 4 cystic/4 frontal  | 2 subtotal |              |              | 4 HG   |
|                            |                    |       |                           | 1 parietal          |                      |              |              |       |
|                            |                    |       |                           | 1 temporal          |                      |              |              |       |
|                            |                    |       |                           | 1 third ventricle   |                      |              |              |       |
|                            |                    |       |                           | 1 fourth ventricle  |                      |              |              |       |
| Kaji et al., 2006[29]      | 1                  | 17   | Headache                  | Solid/frontal       | Total | 60 Gy        | Etoposide    | HG    |
| Kubota et al., 2006[30]    | 1                  | 8    | Headache                  | Hemorrhagic solid   | Total | 40 Gy        |              | HG    |
| Miranda et al., 2006[31]   | 1                  | 43   | Headache                  | Solid        | Total |              |              | LG    |
| Lau et al., 2006[32]       | 1                  | 21   | Headache                  | Solid cystic/parietal | Total |              |              | LG    |
| Hata et al., 2006[33]      | 1                  | 16   | Headache                  | Cystic/parietal    | Total |              |              | LG    |

Contd...
| Reference               | Gender male/female | Age      | Symptoms                  | Radiology/location | Surgery | Radiotherapy | Chemotherapy       | Grade |
|------------------------|--------------------|----------|---------------------------|--------------------|---------|--------------|---------------------|-------|
| Alaraj et al., 2007[34]| 1                  | 33       | Headache                  | Hemorrhagic        | Total   | 54 Gy        |                     | LG    |
|                        |                    |          | Nausea                    | Solid/temporal     |         |              |                     |       |
|                        |                    |          | Headache                  | Hemorrhagic solid/frontal | Subtotal | 36 GyLg |                     |       |
| Bell et al., 2007[30]  | 1/11               | 0-50 mean20 | Headache                  | 9 solid cystic    | 7 total | 2 patients | 1 patient           |       |
|                        |                    |          |                           | 2 solid            | 4 total |             |                     |       |
|                        |                    |          |                           | 4 frontal          | 4 subtotal|         |                     |       |
|                        |                    |          |                           | 5 parietal         |         |             |                     |       |
|                        |                    |          |                           | 3 extra-axial      |         |             |                     |       |
|                        |                    |          |                           | 1 temporal         |         |             |                     |       |
|                        |                    |          |                           | 2 intraventricular |         |             |                     |       |
|                        |                    |          |                           | Solid cystic/parietal | Total | 66 Gy     | Temozolomide       | HG    |
|                        |                    |          |                           |                    |         |              |                     |       |
|                        |                    |          | Vomiting                  |                    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Fathi et al., 2008[36] | 1                  | 53       | Headache                  | Solid cystic/parietal | Total | 54 Gy | Temozolomide     | HG    |
|                        |                    |          | Vomiting                  |                    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Denaro et al., 2008[37] | 1                | 6        | Headache                  | Solid cystic/    | Total   | 54 Gy | Cisplatin Etoposide | HG    |
|                        |                    |          | Vomiting                  | intraventricular  |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Eom et al., 2008[38]   | 1                  | 20       | Headache                  | Solid cystic/temporal | Total | 54 Gy | Cisplatin Etoposide | HG    |
|                        |                    |          | Hemiparesis               |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Unal et al., 2008[39]  | 1                  | 4        | Headache                  | Solid cystic/      | Total   | 59.4 Gy | Cisplatin Etoposide | HG    |
|                        |                    |          | Ataxia                    | parietal           |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Ganapathy et al., 2009[35] | 1          | 12       | Headache                  | Solid/intraventricular | Total | 66 Gy | Temozolomide     | HG    |
|                        |                    |          | Vomiting                  |                    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Notarianni et al., 2008[9] | 1         | 20       | Headache                  | Cystic/brainstem  | Total   | 54 Gy | Cisplatin Etoposide | HG    |
|                        |                    |          | Ataxia                    |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Kantar et al., 2009[40] | 1                  | 7        | Headache                  | Solid cystic/parietal | Subtotal | 59.4 Gy | Cisplatin Etoposide | HG    |
|                        |                    |          | Ataxia                    |                    |         |              |                     |       |
| Kemerdere et al., 2009[41] | 2      | 6-7 mean6.5 | Headache                  | Solid cystic/1    | 2 total | 2 HG |                      |       |
|                        |                    |          | Vomiting                  | frontoparietal    |         |              |                     |       |
|                        |                    |          | Seizures                  | 1 parietal        |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Salvati et al., 2009[4] | 2/4               | 27-50 mean37 | Headache                  | Solid cystic/2    | 4 total | 60 Gy | 2 temozolomide | 3 LG  |
|                        |                    |          | Vomiting                  | frontal occipital |         |              |                     |       |
|                        |                    |          | Seizures                  | 2 temporal        |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Mastrangelo et al., 2010[42] | 2     | 12-21    | Headache                  | Solid/1 frontoparietal | 1 total | Yes |                      | HG    |
|                        |                    |          | Vomiting                  | 1 temporal        |         |              |                     |       |
|                        |                    |          | Seizures                  | 1 subtotal        |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Bergkasa et al., 2011[43] | 1          | 50       | Headache                  | Solid/frontal     | Total   | 54 Gy | Procarbazine CCNU | HG    |
|                        |                    |          | Vomiting                  |                    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Bhattacharjee et al., 2011[44] | 1      | 4        | Headache                  | Solid cystic/     | Total   | 54 Gy | Procarbazine CCNU | HG    |
|                        |                    |          |                           | parieto-occipital |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Agarwal et al., 2012[45] | 1                  | 12       | Headache                  | Solid/parietal    | Total   | 54 Gy | Procarbazine CCNU | HG    |
|                        |                    |          | Vomiting                  |                    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Khosla et al., 2012[46] | 1                  | 11       | Headache                  | Solid cystic/     | Total   | 54 Gy | Procarbazine CCNU | HG    |
|                        |                    |          | Vomiting                  | frontoparietal    |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |
| Nasit and Trivedi, 2013[46] | 1          | 10       | Headache                  | Solid cystic/     | Total   | 54 Gy | Procarbazine CCNU | HG    |
|                        |                    |          | Vomiting                  | frontal parietal  |         |              |                     |       |
|                        |                    |          | Seizures                  |                    |         |              |                     |       |
|                        |                    |          |                           |                    |         |              |                     |       |

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Astroblastoma tends to be peripherally oriented and may involve from the ventricular system. In these instances, additional imaging of neural axis should be considered to rule out drop metastasis. Although rim enhancement seen around its cystic components may resemble that of a necrotic GBM, astroblastomas usually have a minimal peritumoral white matter T2 prolongation. Janz and Buhl refer the extent of peritumoral edema as carrying an unfavorable radiological feature that suggested early recurrence or progression in astroblastoma, even when if pathology is consistent with low grade. The authors showed a recurrence rate of 23.5% in high grade and 60% in low grade.

In a review of 85 patients by Sughrue et al., those undergoing gross total resection (GTR) experienced improved survival compared to those undergoing subtotal resection with 855 survival at 5 years in the GTR group versus 55% in the subtotal resection group. Mangano et al. analyzed outcomes and treatment strategies in low- and high-grade astroblastomas: among the patients with high-grade tumors, those who received surgery and radiotherapy had the highest survival rate. Table 1 summarizes the various case report and literature since 1975.

Features suggestive of high-grade/malignant lesions include the extent of peritumoral T2 signal on MRI, cytological atypia, high Ki-67 index, tumor necrosis, increased cellularity, and vascular proliferation. These prognostic factors are not always applicable. Janz and Buhl present a case in which there was an early recurrence of a low-grade
variant that required postoperative radiotherapy with no further recurrence.[36] Lau et al. and Yao et al. described a low-grade astroblastoma treated with GTR that recurred at 12 and 20 months requiring another surgery followed by postoperative radiotherapy.[32,39] Dereck et al have demonstrated a case of low grade astroblastoma showing signs of recurrence with leptomeningeal spread and in that case radiotherapy was delivered.

Optimal treatment modality for astroblastomas is not clear since it being a rare tumor. GTR is the best treatment offered to the patients whenever possible since it provides excellent tumor control rates and subtotal resection should be avoided.[17,38] Addition of post operative adjuvant focal radiotherapy after subtotal resection does not compensate for gross tumor resection and hence gross tumor resection is the standard as far as safely achievable. Adjuvant therapy for high-grade and recurrent cases is recommended.[17] The authors have tried various chemotherapeutic drugs in the form of temozolomide, cisplatin, etoposide, cyclophosphamide, and bevacizumab without much success. Regular follow-up is necessary even in low-grade variants due to unpredictable disease course. Well-circumscribed tumors which have undergone total resection carry a favorable prognosis. Ahmed et al. have published the largest series of 239 patients and concluded that supratentorial location, age >60 years at diagnosis, and treatment before 1990 were correlated with decreased survival.[35]

Conclusion
Astroblastoma is an extremely rare primary brain neoplasm. Since it shares features with other brain tumors, the diagnosis is often challenging. Its histogenesis is still not clear and confusion persists regarding its classification among other brain tumors. Because of its rarity of occurrence, it is difficult to conduct studies to explore its tumor characteristics. The treatment is variable without any standardization. Although the surgical resection in terms of GTR is recommended, there is variable use of postoperative adjuvant radiotherapy and chemotherapy. It has an unpredictable biological course with an increased risk of recurrence and rapid progression. Case reports like this help disseminate knowledge on uncommon tumors with insights on diagnostic and treatment challenges.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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