Int J Clin Exp Pathol 2015;8(6):7450-7456
www.ijcep.com /ISSN:1936-2625/IJCEP0008420

Case Report

Distant dissemination of mixed low-grade astroblastoma-arteriovenous malformation after initial operation: a case report

Kun Yao[1*], Bin Wu[2*], Mei Xi[3], Zejun Duan[1], Jiqiang Wang[2], Xueling Qi[1]

[1]Department of Pathology, Beijing San Bo Brain Hospital, Capital Medical University, Haidian District, Beijing, P. R. China; [2]Department of Neurosurgery, Beijing San Bo Brain Hospital, Capital Medical University, Haidian District, Beijng, P. R. China; [3]Department of Neurology, Beijing San Bo Brain Hospital, Capital Medical University, Haidian District, Beijng, P. R. China. [*]Equal contributors.

Received March 25, 2015; Accepted May 20, 2015; Epub June 1, 2015; Published June 15, 2015

Abstract: We present a rare case of low-grade astroblastoma coexisting with an arteriovenous malformation (AVM) underwent surgery two times in a 38-year-old man. After the first surgery, this case was reported as a mixed low-grade astroblastoma and AVM. The lesion was completely resected surgically along with AVM. The patient underwent postoperative radiotherapy. Twenty months later, MRI showed enhanced lesions in suprasellar, pineal region and multiple small lesions in the spinal cord, whereas completely no recurrent lesion at the primary tumor site. So, the patient rationally underwent surgical removal in suprasellar and pineal region. After the second surgery, this case was diagnosed as a high-grade astroblastoma. Cells from the second surgical specimens showed high MIB-1 index and an increased olig-2 index. In addition, it is not common for low-grade astroblastoma metastasis to suprasellar, pineal region and spine with completely no recurrence at the original primary tumor site. Therefore it is difficult to predict tumor behavior and patient's clinical outcome merely based on histologic features. The important issue is whether the AVM was thought to be the cause of poor progress of this tumor. More cases are needed to confirm this. Classification and histogenesis of this tumor is still debated. Lack of clinicopathological correlation makes the prognosis of this tumor unpredictable. Anyway, we should be very discreet to treat the astroblastoma, even for low-grade astroblastoma.

Keywords: Arteriovenous malformation, astroblastoma, dissemination, prognosis, treatment

Introduction

Astroblastoma was first described by Bailey in the early 20th century, due to the rarity of this tumor, little is known about its biologic behavior prognosis and the appropriate course of treatment [1]. This rare type of glial tumor occurs most frequently in young adults and is estimated to account for 0.45%-2.8% of primary gliomas [1, 2]. Low incidence of astroblastomas has resulted in little information on clinical outcome data and standardized treatment protocols.

We are reporting a rare case of mixed low-grade astroblastoma-arteriovenous malformation in a previously healthy man which developed dissemination to the suprasellar, pineal region and spine after initial first time gross total resection.

Clinical summary

A 36-year-old man presented in our hospital for the first time in March 2013 with a 6-day history of headache, nausea and vomiting, and his headache in the area of right frontotemporal lobe had worsened for the past three days prior to admission. Cranial computed tomography (CT) scan revealed right occipital lobe hemorrhage (**Figure 1A**). The CT-angiography and digital subtraction angiography revealed right posterior cerebral artery malformation associated with an aneurysm (**Figure 1B** and **1C**). Then the patient received right parieto-occipital craniotomy, which revealed a highly hemorrhagic dark-

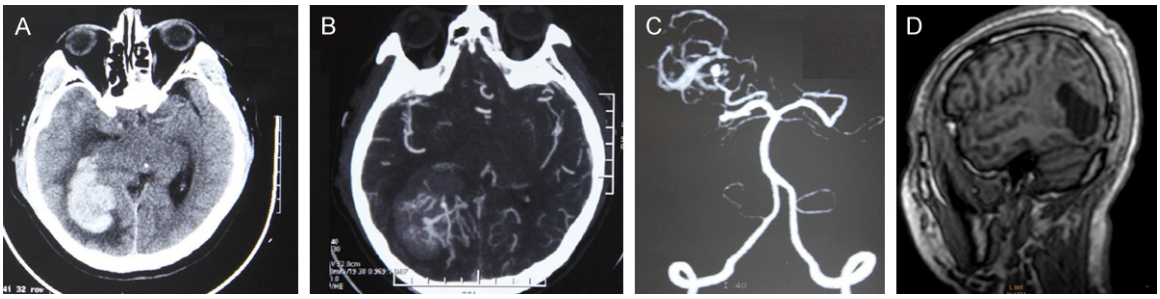

Figure 1. A. Pre-operative computed tomography scan image showing acute intracerebral bleeding in the right occipital lobe. B and C. The computed tomography angiography and digital subtraction angiography examination showed right posterior cerebral arteriovenous malformation associated with aneurysm. D. Post-operative brain magnetic resonance imaging (T1).

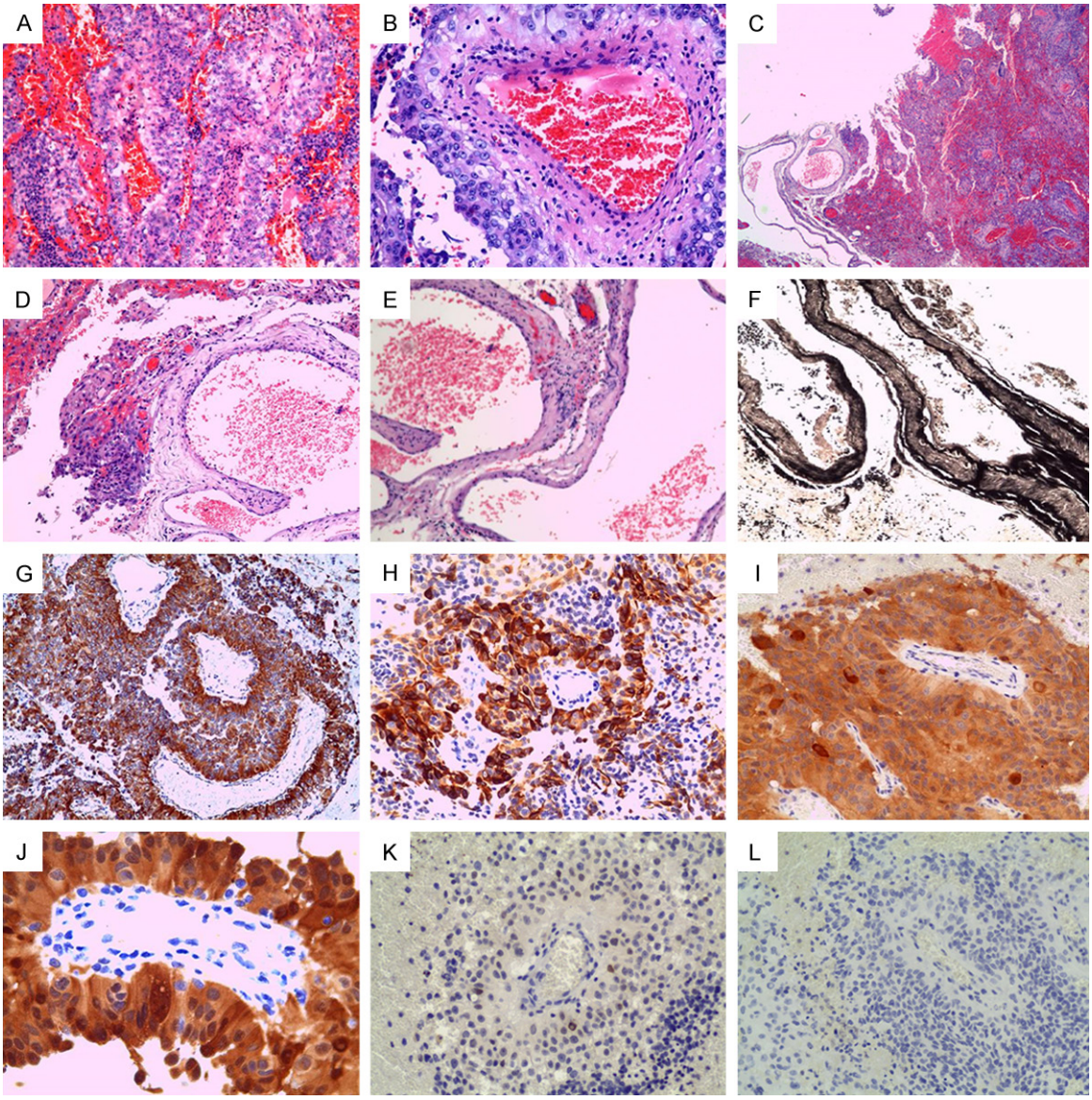

Figure 2. A and B. Well-developed perivascular pseudorosettes are seen throughout the tumor (H and E, × 200, × 400). C-E. Abnormal, tortuously distributed vessels characteristic of an arteriovenous malformation aggregated with the tumor. F. Elastic fiber stain. G. Vimentin stain. H. GFAP stain. I. VEGF stain. J. NSE stain. K. Part of the tumor cells were positive for Olig-2. L. Negative for EMA.

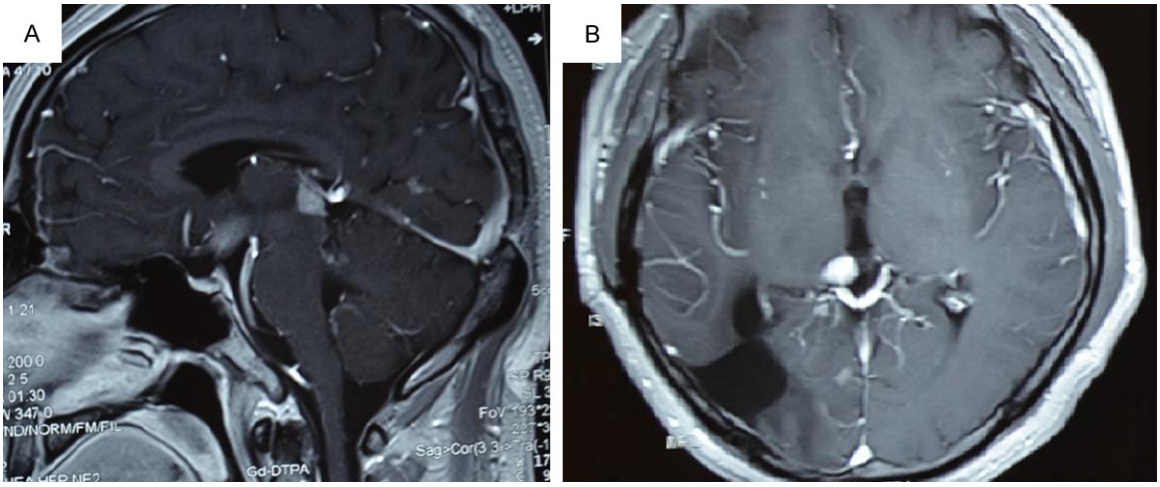

Figure 3. Sagittal (A) and Axial (B) magnetic resonance images with gadolinium enhancement of the patient 20 months after the initial operation demonstrating Metastasis of tumor in suprasellar and pineal region, but no recurrence or residual tumor at the primary tumor site.

red lesion in the temporo-occipital cortex with abnormal surrounding vessels. The lesion was well-circumscribed pushing borders and it was completely resected surgically along with vascular malformation.

On gross examination, the surgical specimen was soft, dark-red. The result of the pathologic examination of the tumor was consistent with astroblastoma, in the same area, abnormal and tortuously distributed vessels. We observed single and multiple layers of tumor cells formed prominent pseudorosettes around blood vessels, with short and thick cytoplasmic processes oriented toward central blood vessels (**Figure 2A**, **2B**). Patchy hemorrhage was observed. In the same area, abnormal and tortuously distributed vessels (**Figure 2C-E**). These vessels were of markedly variable caliber and irregular wall thicknesses with fibromuscular hyperplasia of the media (**Figure 2D** and **2E**). Elastic fibers could be seen on the elastic fiber staining in the arterial malformation (**Figure 2F**). There was no appreciable mitotic activity. Immunohistochemical analysis demonstrated the tumor cells were immunoreactive for vimentin (**Figure 2G**), glial fibrillary acidic protein (GFAP) (**Figure 2H**), vascular endothelial growth factor (VEGF) (**Figure 2I**) and neuron specific enolase (NSE) (**Figure 2J**). Part of the tumor cells were positive for Olig-2 (**Figure 2K**) But they were negative for EMA (**Figure 2L**), synaptophysin, neurofilament protein (NFP), and pancytokeratin. The MIB-1 labeling index was less than 2%. The histological diagnosis was mixed low-grade astroblastoma-arteriovenous malformation. Postoperative MR imaging showed no residual tumor (**Figure 1D**). The post-operative course was uneventful. The patient underwent postoperative radiotherapy for a total dose of 54 Gy in 30 fractions.

After a twenty-month disease-free interval, the patient came to our hospital again in December 2014, complaining about eye abduction on right side and left homonymous hemianopia. So, he was rehospitalized for further evaluation. MRI scan showed enhanced lesions in suprasellar and pineal region (**Figure 3A** and **3B**). Spinal MRI of the patient demonstrated multiple small enhanced lesions in the spinal cord (cervical, thoracic and lumbar) (**Figure 4**). Surprisingly, MRI showed completely no residue or recurrent tumor at the original primary tumor site. The enhanced lesions in suprasellar and pineal region were totally resected together by a right frontal craniotomy via the corpus callosum fornix. Histological examination showed the tumor contained neoplastic cells with astroblastic arrangements. A striking perivascular array of pseudorosettes was also found (**Figure 5A**). The cell nuclei w ere irregular, prominent and hyperchromatic, and mitotic figures may be seen. The tumor cells exhibited diffuse staining for vimentin (**Figure 5B**). VEGF (**Figure 5D**), NSE (**Figure 5E**) and Olig-2 (**Figure 5G**). Part of the tumor cells were positive for GFAP (**Figure 5C**). And they were negative for

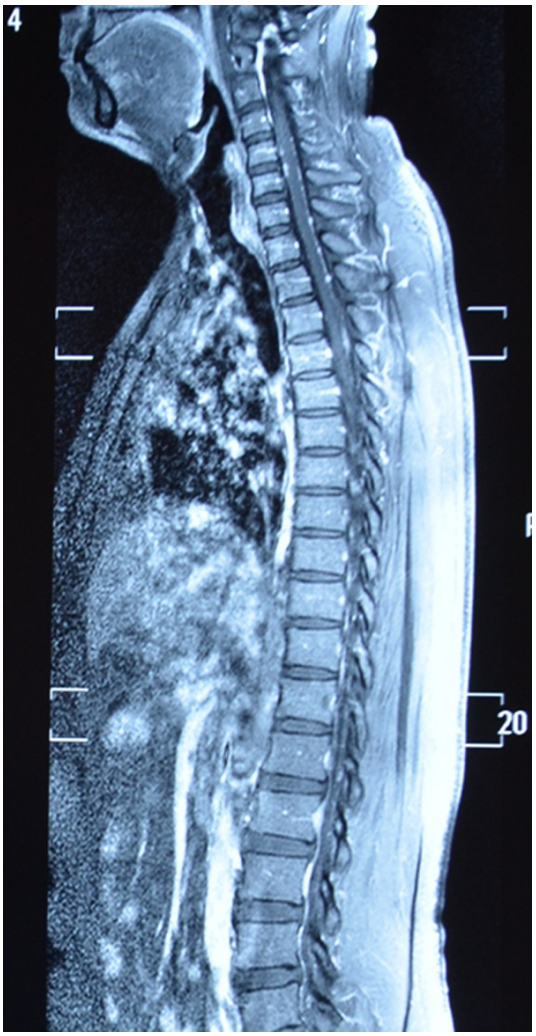

Figure 4. Sagittal cervical, thoracic and lumbar MRI of the spine revealing multiple tumor metastasis along the whole spinal canal 20 months after the initial operation.

EMA (**Figure 5F**), synaptophysin, NFP, and pan-cytokeratin. Analysis of MIB-1 immunoreactivity within the tumor showed a MIB-1 labeling index of approximately 30% (**Figure 5H**). In the end, the diagnosis of anaplastic astroblastoma was rendered.

Genetic findings

MGMT promoter status was assessed by methylation-sensitive high resolution melting (MS-HRM). Genomic DNA was extracted from formalin-fixed and paraffin-embedded tissues using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. PCR amplification and HRM were performed on LC480 (Roche Applied Science) as adapted from the published protocol by Wojdacz and Dobrovic [3].

EGFR/CEP7 probe set (Vysis/Abbott Molecular) was used to identify EGFR amplification. Status of deletion of 1p, 19q, 10q deletion and was evaluated by using probes of 1p36/1q25, 19q13/19p13 and PTEN/CEP10 (all probes were from Vysis/Abbott Molecular). Fixed, paraffin-embedded tumor tissue was treated according to standard protocols and 300 interphase cells were scored. Amplification of EGFR was defined as ratio of EGFR signal to CEP7 signal equal to or greater than two. At least 30% or more increase in nuclei numbers was necessary for a signal to be scored as a deletion.

The methylation level of the MGMT promoter was 15-20%. There was no evidence of chromosome 1 p, 19 q and 10 q deletion (**Figure 5**). No EGFR gene amplification was found.

The patient was administered 60 Gy radiation therapy and chemotherapy with temozolomide (TMZ) for this spinal metastasis after the second surgery. At present he is doing well without neurological deficits and latest follow-up MRI detected no recurrence of the tumor 4 months later after the second operation.

Discussion

It was described that most cases of astroblastoma were frequently seen in children and young adults like in this case. The first reported case on astroblastoma was by Bailey and Bucy in 1930 [4]. They believed that astroblastoma originated from astroblasts, an intermediate stage between glioblasts and astrocytes. A study using electron microscopy proved that tumor cells of astroblastoma are intermediate between astrocytes and ependymal cells, and thus the possible presence of tanycytes was presented as the origin of astroblastoma [5, 6]. Histopathology showed characteristic perivascular pseudorosettes. Not like the perivascular pseudorosettes in ependymoma, those in astroblastoma had short and thick cytoplasmic processes. Tumor cells were strongly immunoreactive for NSE, GFAP, and vimentin and the amount of hyaline varied from case to case [7]. In our case, papillary perivascular pseudorosettes with short and thick cytoplasmic processes oriented toward central blood vessels

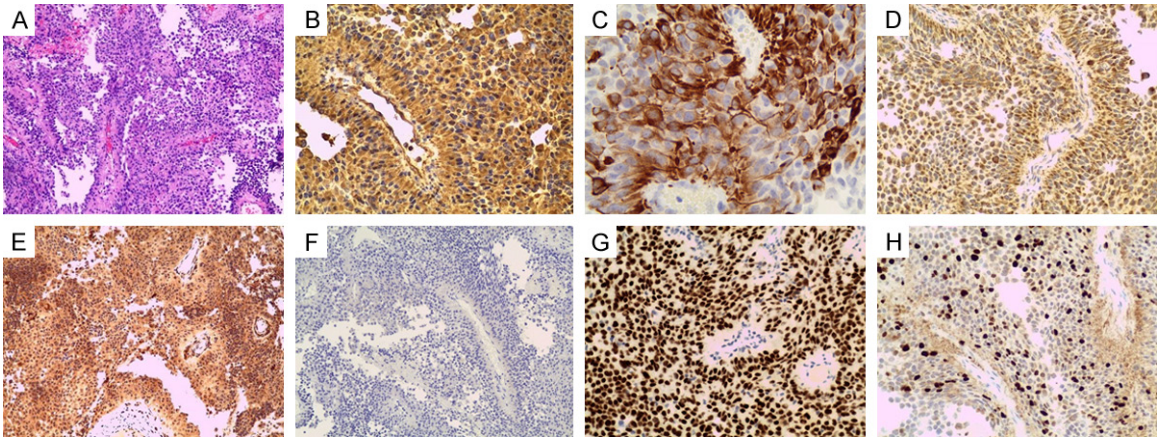

Figure 5. A. Well-developed perivascular pseudorosettes are seen throughout the tumor (H and E, × 200). B. Vimentin stain. C. GFAP stain. D. VEGF stain. E. NSE stain. F. EMA stain. G. Olig2 stain. H. MIB-1 labeling index was up to 30%.

were distributed diffusely throughout the tumors from both the first and second surgical and surgical specimens. As to immunohistochemistry, tumor cells were all immunoreactive for NSE, GFAP and vimentin, and negative for EMA and CK in specimens from the two times of surgery. All of these characteristics supported the diagnostic of astroblastoma in two times of surgery.

The interesting feature of the present case is that some tumor cells in the second surgical specimens lost GFAP expression. On the contrary, the increase in Olig-2 immunoreactivity was found in the second surgical specimens. Olig-2 is required for neuron and oligodendrocyte differentiation, and it blocks astrocyte differentiation [8]. Setoguchi et al. demonstrated that the accumulation of Olig-2 in the nucleus of neural stem cells blocks ciliary neurotrophic factor-induced astrocyte differentiation [9]. These experimental reports suggest that increase in Olig-2 immunoreactivity may have led to the loss in GFAP reactivity in the present case. Genetic alterations in astroblastoma, including loss of heterozygosity (LOH) of 9p, LOH of 19q, and abnormalities in chromosome 10, 19, 21 and 22 observed in some cases of astroblastoma [5, 7, 10] have been reported. None of the detected gains or losses of chromosomes was specifically necessary for malignancy in astroblastoma. It is well known that LOH of 19q is very important in oligodendroglioma tumorigenesis and 10q deletion (PTEN) and EGFR amplification occur frequently in high-grade glioma in adults. Although it is not apparent whether these genetic alterations are related to our case of astroblastoma, it may still be of interest to examine this aspect. So, we did some genetic examinations, such as 1p/19q deletion, 10q deletion and EGFR amplification. However none of such genetic alterations are found in this case.

Astroblastomas still remain as rare and controversial tumors with variable clinical outcomes and unknown cellular origin. According to histological findings, they were classified into low grade and high grade. Low-grade astroblastomas included astroblastomas with uniform perivascular arrangement of pseudorosettes, low to moderate numbers of mitotic figures and minimal cellular atypia. Gross total resection of sharply circumscribed astroblastomas may result in long-term survival [2]. High-grade astroblastomas have anaplastic features, cytological atypia and a high MIB labeling index. Based on these criteria, we have diagnosed this case as the low-grade subtype after the first operation, as suggested by the low MIB-'I labeling index (2%). In addition, it was a rare situation that the occurrence of two different lesions, astroblastoma and a vascular malformation, was discovered at the same time and in the same location. So the final histological diagnosis for the first time was mixed low-grade astroblastoma and arteriovenous malformation. The lesion in this case was found well-circumscribed with pushing borders during the first surgery. It enabled us to remove the lesion completely. So, postoperatively only radiotherapy was performed for a total dose of 54 Gy in

30 fractions after the first operation. We did not administer adjuvant chemotherapy therapy after the initial gross total resection.

Twenty months later, MRI showed an apparently dissemination in the suprasellar, pineal region and spine, whereas no recurrent tumor at the primary tumor site. Our patient exhibited essential histological pattern of high-grade astroblastoma for the second time of surgery. Anaplastic histology is associated with tumor recurrence and progression, suggesting that more aggressive treatment is necessary for high-grade lesions [11, 12]. Salvati M *et al.* proposed an aggressive standardized treatment for those lesions that meet anaplastic criteria. Owing to their postulated glial origin and the propensity to have aggressive courses, they advocate the use of a safe adjuvant chemotherapeutic regimen with TMZ, used concomitantly and subsequently to radiotherapy, especially for the high-grade asroblastoma cases [2]. Recently, a retrospective case series suggested MGMT promoter hypermethylation were correlated with a survival benefit from TMZ in patients with recurrent anaplastic astrocytoma [13]. So we applied methylation-sensitive high resolution melting (MS-HRM) analysis to quantify MGMT methylation in this case. The degree of MGMT methylation was 15-20% in our case. We advocated the patient chemotherapy with TMZ and 60 Gy radiation therapy after the second surgery.

It is not rare for low-grade astroblastoma to recur and progress at the primary tumor site, but dissemination to suprasellar, pineal region and spine with no recurrence at the primary tumor site. Our patient had a low-grade astroblastoma with AVM for the first surgery. So, we suspected the poor progress and dissemination of this tumor might somehow be related to AVM and overexpression of VEGF. Indeed, overexpression of VEGF was found in the endothelial layer of AVM vessels and tumor cells in the first surgery and second surgical specimens. VEGF was responsible for endothelial cell replication, migration, differentiation and survival, and might also mediate vascular remodeling [14]. Thus, we thought VEGF secreted by tumor cells bound to endothelial cells and might activate neo-angiogenesis. It appeared that VEGF might be the possible underlying factor for the occurrence of both AVM and astroblastoma at the same site during the first operation. Moreover, VEGF overexpression typically indicates a poor prognosis for patients with many cancers [15, 16] and increased expression of VEGF was correlated with the metastasis and dissemination of many types of tumor [15, 16]. Therefore concurrent overexpression of VEGF and AVM seems essential to predict anaplastic behavior of low-grade astroblastoma. However, it is necessary to study more cases to confirm this.

Because of the rarity of astroblastomas, no consensus has been reached regarding to their optimal management. Some suggested [11] that the best clinical results were obtained after total or subtotal resection of the tumor, followed by radiotherapy. Other believed that total resection of these tumors should be a therapeutic goal, since no recurrence of the tumor was found in the short term [7]. Caroli *et al*. reported a high-grade astroblastoma with a 5-year survival without recurrence after total resection, radiation therapy, and TMZ usage [17]. In our case, the initial total removal and radiotherapy both failed to inhibit the metastasis of tumor. We advocated the patient use of chemotherapy and radiation therapy after the second surgery for this spinal dissemination. Longer patient follow-up and clinical studies would further clarify the real behavior of astroblastoma and its ideal management.

Acknowledgements

This work was supported by Basic and Clinical Cooperation Project of Capital Medical University (15JL89) and *Capital Health Research and Development of special* (Grant No. 2011-1020-01).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xueling Qi, Department of Pathology, Beijing San Bo Brain Hospital, Capital Medical University, Haidian District, Beijing, P. R. China. E-mail: xszqxl169@163.com

References

[1] Navarro R, Reitman AJ, de Leon GA, Goldman S, Marymont M, Tomita T. Astroblastoma in childhood: pathological and clinical analysis. Childs Nerv Syst 2005; 21: 211-220.

[2] Salvati M, D'Elia A, Brogna C, Frati A, Antonelli M, Giangaspero F, Raco A, Santoro A, Delfini R. Cerebral astroblastoma: analysis of six cases and critical review of treatment options. J Neurooncol 2009; 93: 369-378.
[3] Balic M, Pichler M, Strutz J, Heitzer E, Ausch C, Samonigg H, Cote RJ, Dandachi N. High Quality Assessment of DNA Methylation in Archival Tissues from Colorectal Cancer Patients Using Quantitative High-Resolution Melting Analysis. J Mol Diagn 2009; 11: 102-107.
[4] Bailey P, Bucy P. Astroblastomas of the brain. Acta Psychiatr Scand 1930; 5: 439-61.
[5] Jay V, Edwards V, Squire J, Rutka J. Astroblastoma: Report of a case with ultrastructural, cell kinetic, and cytogenetic analysis. Pediatr Pathol 1993; 13: 323-32.
[6] Rubinstein LJ, Herman MM. The astroblastoma and its possible cytogenic relationship to the tanycyte. An electron microscopic, immunohistochemical, tissue- and organ-culture study. Acta Neuropathol 1989; 78: 472-83.
[7] Brat DJ, Hirose Y, Cohen KJ, Feuerstein BG, Burger PC. Astroblastoma: Clinicopathologic features and chromosomal abnormalities defined by comparative genomic hybridization. Brain Pathol 2000; 10: 342-52.
[8] Takebayashi H, Nabeshima Y, Yoshida S, Chisaka O, Ikenaka K, Nabeshima Y. The basic helix-loop-helix factor olig2 is essential for the development of motoneuron and oligodendrocyte lineages. Curr Biol 2002; 12: 1157-1163.
[9] Setoguchi T, Kondo T. Nuclear export of OLIG2 in neural stem cells is essential for ciliary neurotrophic factor-induced astrocyte differentiation. J Cell Biol 2004; 166: 963-968.
[10] Shuangshoti S, Mitphraphan W, Kanvisetsri S, Griffiths L, Navalitloha Y, Pornthanakasem W, Mutirangura A. Astroblastoma: report of a case with microsatellite analysis. Neuropathology 2000; 20: 228-232.
[11] Bonnin JM, Rubinstein LJ. Astroblastomas: A pathological study of 23 tumors, with a postoperative follow-up in 13 patients. Neurosurgery 1989; 25: 6-13.
[12] Thiessen B, Finlay J, Kulkarni R, Rosenblum MK. Astroblastoma: does histology predict biologic behavior? J Neurooncol 1998; 40: 59-65.
[13] Sadones J, Michotte A, Veld P, Chaskis C, Sciot R, Menten J, Joossens EJ, Strauven T, D'Hondt LA, Sartenaer D, Califice SF, Bierau K, Svensson C, De Grève J, Neyns B. MGMT promoter hypermethylation correlates with a survival benefit from temozolomide in patients with recurrent anaplastic astrocytoma but not glioblastoma. Eur J Cancer 2009; 45: 146-153.
[14] Moftakhar P, Hauptman JS, Malkasian D, Martin NA. Cerebral arteriovenous malformations. Part 1: Cellular and molecular biology. Neurosurg Focus 2009; 26: E10.
[15] Zhan P, Wang J, Lv XJ, Wang Q, Qiu LX, Lin XQ, Yu LK, Song Y. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: a systematic review with meta-analysis. J Thorac Oncol 2009; 4: 1094-1103.
[16] Chang DF, Xu ZQ, Sun B. Relationship between VEGF protein expression and lymph node metastasis in papillary thyroid carcinoma among Asians: a meta-analysis. Tumour Biol 2014; 35: 5511-5518.
[17] Caroli E, Salavati M, Esposito V, Orlando ER, Giangaspero F. Cerebral astroblastoma. Acta Neurochir 2004; 146: 629-633.