Int J Clin Exp Med 2017;10(9):13458-13462
www.ijcem.com /ISSN:1940-5901/IJCEM0054665

Original Article

Glioblastoma with primitive neuronal component: report of a case and review of literature

Jing Liu[1,2*], Wei Wang[2*], Yongxia Zhang[3], Lei Jiang[2], Guimei Qu[2], Tingguo Zhang[1]

[1]Department of Pathology, School of Medicine, Shandong University, Jinan 250012, Shandong, China; Departments of [2]Pathology, [3]Radiology, Affiliated Yantai Yuhuangding Hospital, Medical College of Qingdao University, Yantai, China. [*]Co-first authors.

Received January 21, 2017; Accepted August 6, 2017; Epub September 15, 2017; Published September 30, 2017

Abstract: According to the 2016 WHO Classification, glioblastoma with primitive neuronal components (GBM-PNC) was added as a pattern in glioblastoma. A 59-year-old woman presented initially with paroxysmal headache at bilateral frontal temporal for a month. Imaging showed a solid cystic mass in the right frontal lobe with a range of 4.7 cm×5.6 cm. She had an operation to excise the occupying lesion in the right frontal lobe. The pathological diagnosis was GBM-PNC by histological and immunohistochemical staining. Also, this case was analyzed for IDH1 (R132) mutation by PCR and pyrosequencing, which showed that it was IDH-wildtype. The prognosis of this type is poor. In addition, literature review was carried out to discuss its clinical manifestation, histological and immunohistochemistry features, differential diagnosis and prognosis.

Keywords: Glioblastoma, primitive neuronal component, isocitrate dehydrogenase 1 (IDH1)

Introduction

Glioblastoma is the most common malignant and most aggressive primary brain tumor in adults. The median age at diagnosis of glioblastoma is 64 years [1]. Glioblastoma with primitive neuronal components (GBM-PNC) is a rare variant of glioblastoma. It poses both diagnostic and therapeutic challenges [2]. According to the 2016 WHO Classification, glioblastoma with primitive neuronal components (GBM-PNC) was added as a pattern in glioblastoma [3]. This pattern of tumor has a tendency for craniospinal fluid dissemination [4]. Despite aggressive treatment with surgery, radiation, and chemotherapy, median survival is only about 15 months [1]. Glioblastomas are divided into (a) glioblastoma, IDH-wildtype (about 90% of cases); (b) glioblastoma, IDH-mutant (about 10% of cases); (c) glioblastoma, NOS, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed in the CNS WHO classification [3]. This report involves a case of GBM-PNC with IDH-wildtype.

Materials and methods

Clinical data

A 59-year-old woman complained of paroxysmal headache, especially at bilateral frontal temporal, with speech disturbance occasionally for a month. She was not accompanied by weakness of limbs, nausea and vomiting and limb seizures. In general, the patient was in relatively mild condition, suffering from lumbar disc herniation for one year.

Magnetic resonance imaging (MRI) showed a solid cystic mass in the right frontal lobe with a range of 4.7 cm×5.6 cm. The solid part of the diffusion image showed a slightly higher signal and the cystic part showed low signal. The boundary was mostly blurred, and the edema signal was seen around. Bilateral ventricles were significantly compressed, midline left offset, corpus callosum pressure showed unclear (**Figure 1**). The patient was diagnosed with right frontal space occupying lesion.

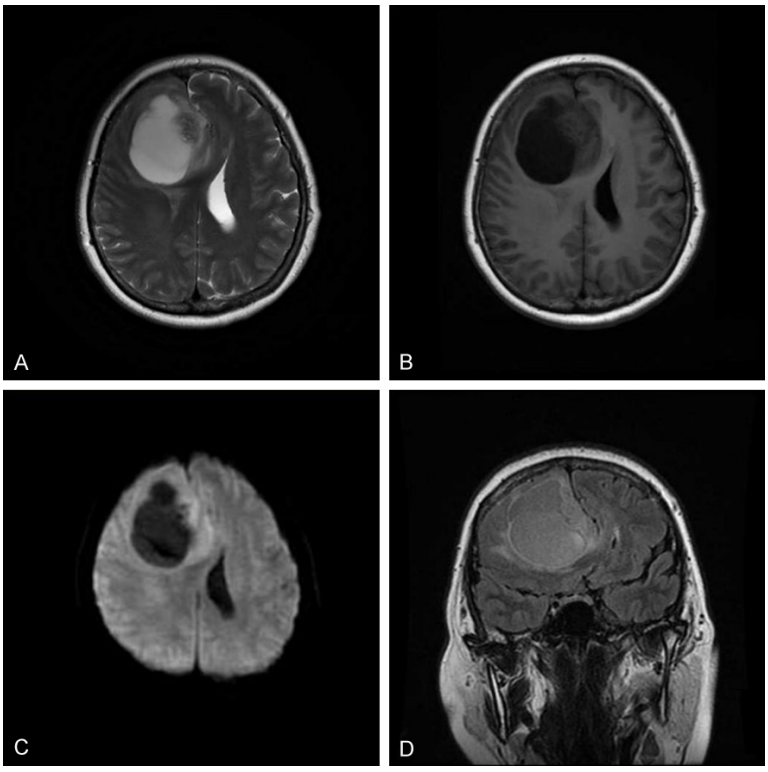

Figure 1. Magnetic resonance imaging (MRI) showed a solid cystic mass in the right frontal lobe with a range of 4.7 cm×5.6 cm. The solid part of the diffusion image showed a slightly higher signal, the cystic part showed low signal. The boundary was mostly blurred, and the edema signal was seen around. A. Axial, T2-Weighted. B. T1-Weighted. C. Diffusion weighted imaging (DWI). D. Enhanced magnetic resonance imaging.

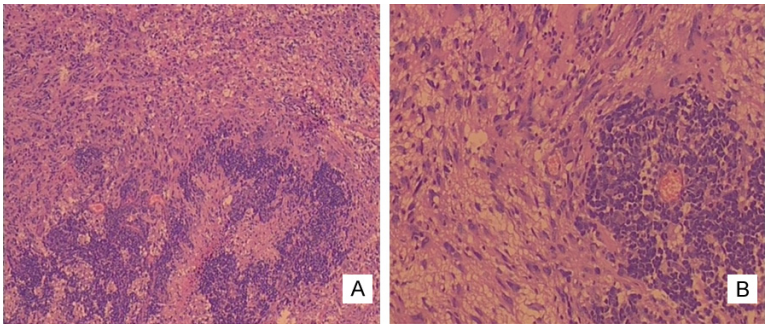

Figure 2. HE staining. A. The glial component in the upper shows bizarre cells with abundant eosinophilic cytoplasm, atypical pleomorphic nuclei and prominent nucleoli were dispersed in a fine fibrillary background; underneath the PNC presents small undifferentiated cells with scant cytoplasm and oval round hyperchromatic nuclei in those areas, highly cellular and minimal or no fibrillary material could be seen in the background (×40). B. Tiny nodules of PNC components locate around blood vessels (×100).

Operation process

Cut on the skin along marked double coronal incision, from skin to subcutaneous tissue. Subperiosteal dissection at the right forehead, then open the skull and dura. Separate the tumor along the periphery. The tumor tissue was cystic solid, and the cyst wall was broken during the process of tumor separation. All the tumor tissues were removed under the microscope, about 6×5×4 cm. The patient left the hospital 13 days after surgery with stable condition.

Methods

The sample was fixed by 4% neutral formalin, embedded in paraffin (FFPE). Four-micrometer thick sections were prepared for hematoxylin and eosin (H&E) and immunohistochemical staining. Immunohistochemical staining (S-P method) adopted GFAP, Vimentin, synaptophysin, CD56, OLIG-2, MIB-1 (Ki67) and S-100, DAB color. There was positive control in every step, which took the known positive slice of the corresponding antibody to make contrast, while negative control replaced the first antibody with PBS. Both the antibodies and kits were purchased from the immunohistochemical staining of ZSGB-Bio.

DNA was isolated from FFPE tissues by using the DNA FFPE Kit (Qiagen, Cat: 180134) according to the manufacturer's protocol. Mutations in IDH1 gene were screened in Genewiz Company by using ABI37-30XL sequence analyzer. The primers for sequencing were: forward primer 5'-GAGCTCTATATGCCATCACTGC-3' and reverse primer 5'-TTCATACCTTGCTTAATGGGTGT-3'.

Results

Grossly, a patch of greyish white tissue measured 5.5 cm×4.5 cm×2.6 cm. The cut surface has a soft, gray appearance.

Microscopically, in approximately 80% of the tumor, bizarre cells with abundant eosinophilic cytoplasm, atypical pleomorphic nuclei and

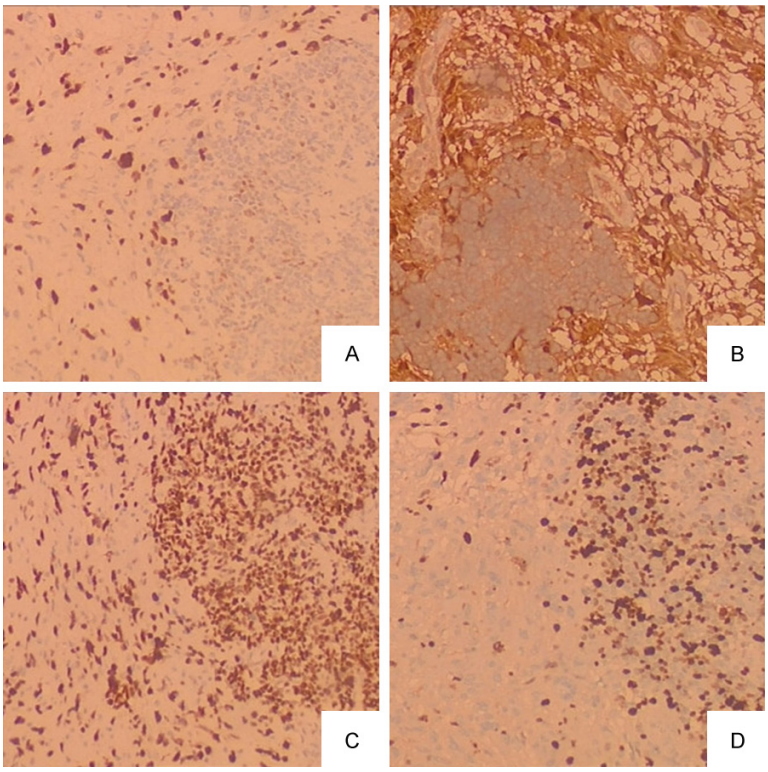

Figure 3. The immunohistochemistry staining (×100) revealed the differences between the two compartments of the tumor. A. The astrocytic component is strongly positive for Olig-2 on the left while PNC is negative for Olig-2 on the right. B. The PNC is negative for S-100 on the lower left while the glial component is positive on the upper right. C. Both the PNC on the left and astrocytic component on the right are strongly immunoreactive for P53. D. The Ki67 proliferation index measured from 10% in the glial regions on the left to 70% in the PNC on the right.

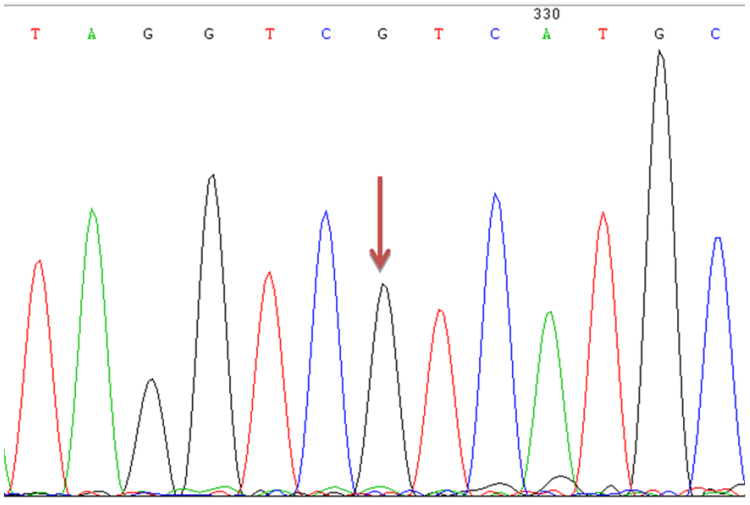

Figure 4. Negative for IDH1 mutation detection: No mutation was found at position 395 of IHD1 gene.

prominent nucleoli were dispersed in a fine fibrillary background. The other component of the tumor consisted of small undifferentiated cells with scant cytoplasm and oval round hyperchromatic nuclei in those areas. In the background, highly cellular and minimal or no fibrillary material could be seen. Focally, tiny nodules of PNC components locate around blood vessels (**Figure 2**).

Immunohistochemical stains with automatic immunostainer (VENTANA) were performed with GFAP, Vimentin, synaptophysin, CD56, P53, OLIG-2, MIB-1 (Ki67) and S-100 antibodies. The tumor revealed different immunoreactivity in the two compartments. The glial component was distinctly positive for GFAP, OLIG2 (**Figure 3A**), S100 (**Figure 3B**), vimentin, P53 (**Figure 3C**) and CD56 antigens. The "small undifferentiated cell" component was negative for GFAP, OLIG2 (**Figure 3A**), S100 (**Figure 3B**), vimentin, synaptophysin and intensely positive for CD56 and P53 (**Figure 3C**). The Ki67 proliferation index measured from 10% in the glial regions to 70% in the small cell compartment (**Figure 3D**).

This case was analyzed for IDH1 (R132) mutation by PCR and pyrosequencing, which showed IDH-wildtype (**Figure 4**).

The patient was treated with temozolomide and radiotherapy after operation and died eight months later after surgery.

Discussion

Glioblastoma is considered to be a grade IV neoplasm. Glioblastoma with primitive neuronal components (GBM-PNC) is a rare variant of glioblastoma, which previously referred to in the literature as glioblastoma with

PNET-like component or malignant glioma with PNET-like features [4-6], the temporal lobe was the most frequent location and about 52% of cases occurred in this area [7]. According to the literature, the median age was 54 years [2, 4, 5]. The occurrence of symptoms was mostly less than six months [4, 8], which was similar to the current case. The tumor was well circumscribed, with significant mass effect, presenting diffuse perilesional edema and rarely (15% of cases) intralesional hemorrhage, necrosis and cystic spaces radiologically [8]. Our present case showed the similar clinical features.

GBM-PNC usually consists of two parts. One is a diffuse astrocytoma of any grade (or oligodendroglioma in rare cases) and the other is well-demarcated nodules containing primitive cells that display neuronal differentiation [3]. For the origin of the PNC component in malignant gliomas, there are two major hypotheses [4]: neuroblastic/neuronal metaplasia and clonal expansion of tumor stem cells or progenitor cells results in PNET-like nodules. In the vascular niches of GBMs, tumor stem cells/progenitor cells have been discovered. This supports the second hypothesis [9, 10]. Our case shows that the tiny nodules of PNC components were located around blood vessels. It seems to be good histological evidence for stem cell/progenitor cell expansion.

Song et al. described that the use of vimentin and CD56 made the diagnosis of GBM-PNC much easier. The expression of GFAP, S100 and vimentin are almost always widespread in the glioma components and it is negative in PNC components. CD56 is strongly and diffusely positive in both, astrocytic and PNC components [2]. The primitive components lack the expression of glial marker (such as GFAP) or present a slight expression [3, 4]. Similar to the above, we also confirm the expression of OLIG2, which is also a glial marker. It's positive in the glial components and negative in the primitive components. The expression of synaptophysin is always a characteristic of the PNC [2-5, 7]. Perry et al. described the largest series cases that synaptophysin staining was present in 87% cases [4] while synaptophysin is negative in our current case.

As far as differential diagnosis, two kinds of diseases including (a) PNET or other small cell embryonal tumors and (b) Small cell GBM should be considered. (a) Despite that PNET or other small cell embryonal tumors may permeate brain parenchyma and might resemble GBM-PNC, an advanced age at diagnosis, existence of a glial area and the reactivity for GFAP, vimentin and OLIG2 immunostain would support a diagnosis of GBM-PNC rather than an embryonal tumor. (b) The distinction of GBM-PNC from the small cell pattern of GBM (SCGBM) is a potential diagnostic confusion [11, 12]. Despite that both tumor types are characterized by cells with high nuclear to cytoplasmic ratios and marked proliferative activity, SCGBM is featured with a diffuse parenchymal infiltrate of monomorphic, deceptively bland oval nuclei, it's more likely to be confused with oligodendroglioma than with PNC [4]. In addition, SCGBM lack the hypercellular nodules, marked hyperchromasia and Homer Wright rosettes features that characterize GBM-PNC. At last, as far as we know, SCGBM has the same risk of CSF seeding as conventional GBMs.

IDH-mutant glioblastoma, which is frequently associated with secondary GBMs and rarely with primary GBMs [13], have a good prognosis than the IDH-wildtype ones [2, 3]. The median overall survival time of the former is more than two times that of the latter [3]. IDH-wildtype glioblastoma account for about 90% of glioblastomas, which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age. The ratio of male-to-female is 1.42:1. Mean length of clinical history is 4 months. Median overall survival is different: with surgery plus chemotherapy and radiotherapy, the median survival is 9.9 months and without chemotherapy it's 15 months [3, 14]. Although treated with surgery plus chemotherapy and radiotherapy, the described case passed away 8 months after operation. The survival time of the patient was less than the median survival, which might be due to IDH-wildtype.

Acknowledgements

Project of Natural Science Foundation of Shandong Province (ZR2016HL39); Yantai Yuhuangding Hospital Youth Research Foundation (201524).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Tingguo Zhang, Department of Pathology, School of Medicine, Shandong University, Jinan 250012, Shandong, China. Tel: +86-13793182978; E-mail: jing0631@hotmail.com

References

[1] Jordan JT, Gerstner ER, Batchelor TT, Cahill DP, Plotkin SR. Glioblastoma care in the elderly. Cancer 2016; 122: 189-197.

[2] Song X, Andrew Allen R, Terence Dunn S, Fung KM, Farmer P, Gandhi S, Ranjan T, Demopoulos A, Symons M, Schulder M, Li JY. Glioblastoma with PNET-like components has a higher frequency of isocitrate dehydrogenase 1 (IDH1) mutation and likely a better prognosis than primary glioblastoma. Int J Clin Exp Pathol 2011; 4: 651-660.

[3] David N, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016; 131: 803-820.

[4] Perry A, Miller CR, Gujrati M, Scheithauer BW, Zambrano SC, Jost SC, Raghavan R, Qian J, Cochran EJ, Huse JT. Malignant gliomas with primitive neuroectodermal tumor-like components: a clinicopathologic and genetic study of 53 cases. Brain Pathol 2009; 19: 81-90.

[5] Kuhn SA, Hanisch UK, Ebmeier K, Beetz C, Brodhun M, Reichart R, Ewald C, Deufel T, Kalff R. A paediatric supratentorial primitive neuroectodermal tumour associated with malignant as-trocytic transformation and a clonal origin of both components. Neurosurg Rev 2007; 30: 143-149.

[6] Miller CR, Perry A. Glioblastoma. Arch Pathol Lab Med 2007; 131: 397-406.

[7] Carmen GE, Emillia M, Iulian R, Ştefan-CL M, Laura S, Alina SS. Pediatric glioblastoma with giant cells and "supratentorial" primitive neuroectodermal component-case report and review of the literature. Rom J Morphol Embryol 2015; 56: 1165-1171.

[8] Kandemir NO, Bahadir B, Gül S, Karadayi N, Ozdamar SO. Glioblastoma with primitive neuroecto-dermal tumor-like features: case report. Turk Neurosurg 2009; 19: 260-264.

[9] Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C, Hamner B, Oh EY, Gaber MW, Finklestein D, Allen M, Frank A, Bayazitov IT, Zakharenko SS, Gajjar A, Davidoff A, Gilbertson RJ. A peri-vascular niche for brain tumor stem cells. Cancer Cell 2007; 11: 69-82.

[10] Gilbertson RJ and Rich JN. Making a tumor's bed: glioblastoma stem cells and the vascular niche. Nat Rev Cancer 2007; 7: 733-736.

[11] Burger PC, Pearl DK, Aldape K, Yates AJ, Scheithauer BW, Passe SM. Small cell architecture-a histological equivalent of EGFR amplification in glioblastoma multiforme. J Neuropathol Exp Neurol 2001; 60: 1099-1104.

[12] Perry A, Aldape KD, George DH, Burger PC. Small cell astrocytoma: an aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. Cancer 2004; 101: 2318-2326.

[13] Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol 2008; 116: 597-602.

[14] Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res 2013; 19: 764-772.