Clin Oncol Cancer Res (2010) 7: 317-321
DOI 10.1007/s11805-010-0538-4

Multicentric Gliomas Misdiagnosed as Metastatic Tumors: One Case Report and Literature Review

Peng WANG[1]
Ming-can WU[1]
Shi-jie CHEN[2]
Yong YANG[2]
Guang-rui ZHAO[1]

[1] Department of Experimental Surgery, Yangtze University Clinical Medical College, Jingzhou 434000, Hubei Province, China.
[2] Department of Neurosurgery, the First People's Hospital of Jingzhou, Jingzhou 434000, Hubei Province, China.

Correspondence to: Shi-jie CHEN
E-mail: cz89@sohu.com,

Received May 26; 2010; accepted October 8, 2010.

E-mail: 2008cocr@gmail.com
Tel (Fax): 86-22-2352 2919

KEY WORDS: multicentric gliomas, glioblastoma, treatment, diagnosis.

Introduction

Multicentric gliomas are considered to be well recognized but uncommon; often scatter widely in different lobes or hemispheres; and cannot be attributed to a definite pathway[1]. A patient diagnosed as multicentric gliomas is presented in this paper. He was firstly misdiagnosed as cerebral metastatic tumors, but later the histopathological examination revealed them to be glioblastoma (WHO grade IV). Additionally, the aim of the paper was to describe the case history of the patient and the problems encountered in the pathogenesis, pathophysiology, diagnosis and treatment.

Case Report

In October 2009, a 44-year-old man visited our hospital, complaining a history of approximately 20 days of headache, nausea, and vomiting and a week earlier, these symptoms became frequent and severe. Apart from some visual deficits, there were no other obvious symptoms during this period of time, and the results of neurological and systemic examinations were completely in normal range. In addition, the magnetic resonance imaging (MRI, Fig.1-9) on brain showed the presence of 2 non-enhancing hypointense or isointense lesions on T1-weighted sequences and hyperintense on T2-weighted sequences, located in both occipital lobes and the area between the left temporal lobe and the hippocampus, with marked edema surrounding the lesions. The contrast MRI revealed 2-3 obvious ring-shaped masses, considered to be cerebral metastatic tumors. The patient then underwent further thorough examinations to find the original tumor, including: chest X-ray, ultrasound examination on visceral organs, blood tests for tumor marks, such as CEA, AFP, TPSA, CA125, CA-199, CA72-4, which all showed negative results.

Based on the rapidly aggravating symptoms and the original diagnosis, a total macroscopic surgery removing the right occipital lesion was performed under general anaesthesia, with the patient in the prone position. During the surgery, the encephalocele was so obvious that the neurosurgeon chose decompressive craniotomy through the right occipital part, in order to avoid the sagittal sinus and transverse

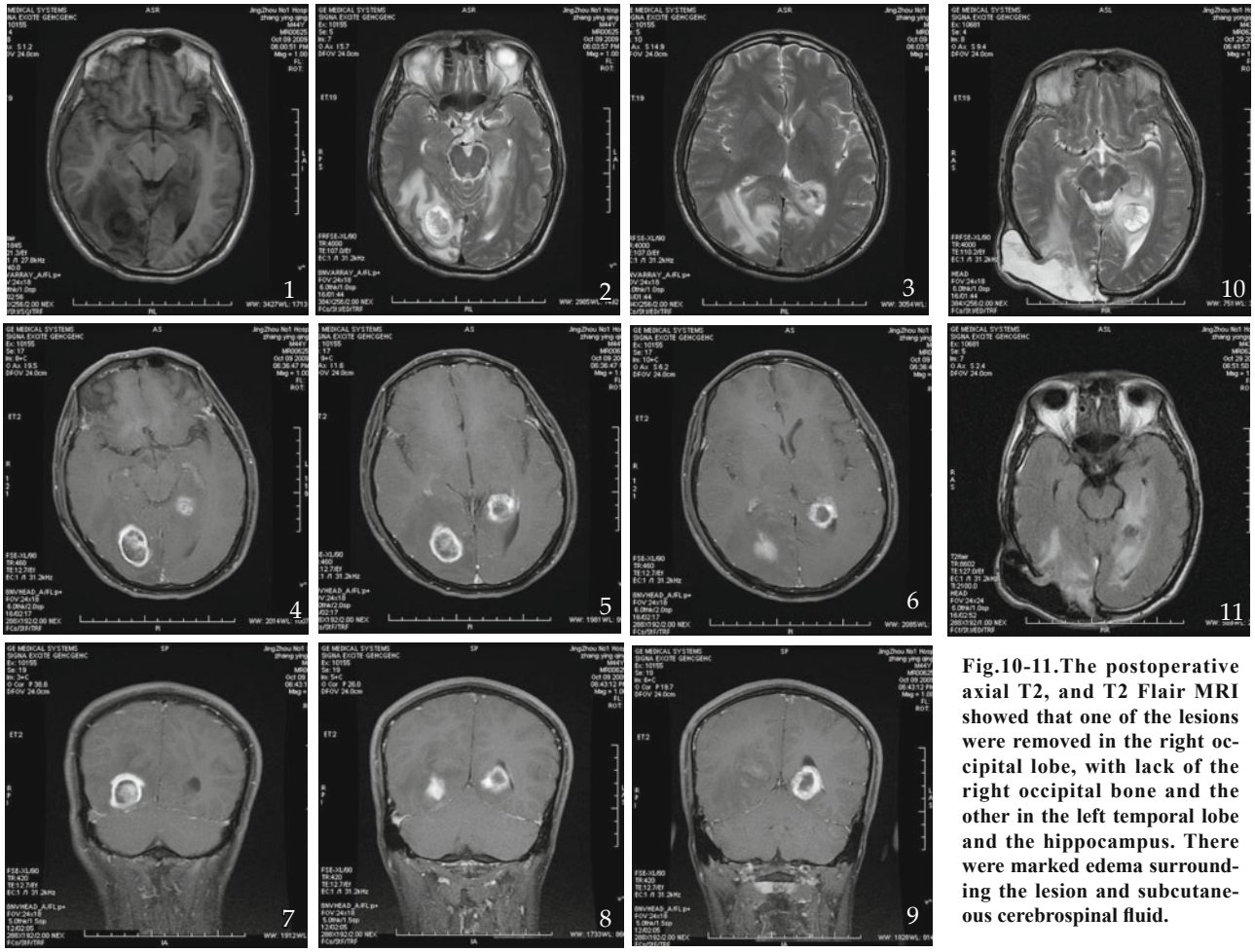

Fig.10-11.The postoperative axial T2, and T2 Flair MRI showed that one of the lesions were removed in the right occipital lobe, with lack of the right occipital bone and the other in the left temporal lobe and the hippocampus. There were marked edema surrounding the lesion and subcutaneous cerebrospinal fluid.

Fig.1-9. The presence of two of non-enhancing hypointense or isointense lesions in T1-weighted sequences (Fig.1) and hyperintense in T2-weighted sequences (Fig.2,3), located in the both occipital lobes and the area between left temporal and hippocampus, with the marked edema surround them, the contrast MRI(Fig. 4-9) revealed 2-3 obivious ring-shaped masses.

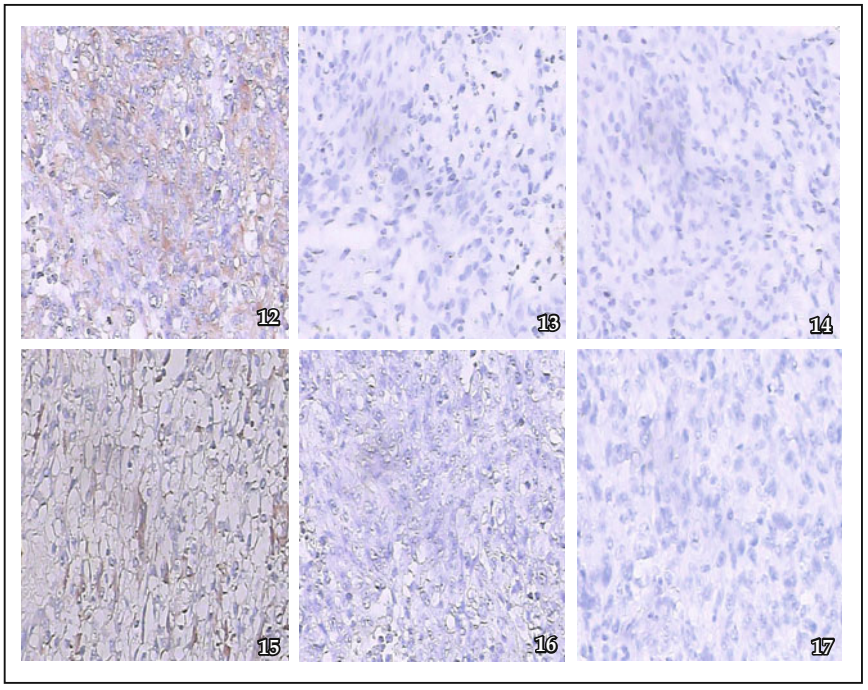

Fig.12-17. The histopathological examination: glioblastoma (WHO grade IV). 12, Vimentin (+); 13, S-100 (-); 14, PCK (-); 15, GFAP (+); 16, EMA (-); 17, CK17 (-).

sinus, to relieve the intracranial hypertension. The right occipital lesion had adequate blood supply and was about 3 cm × 3 cm × 4 cm, with a necrosis inside. The histopathological examination showed that it was glioblastoma (WHO grade IV). The patient's symptoms, such as headache and nausea were relieved for about 2 weeks after the resection of the tumor, except his visual deterioration. Afterwards, the postoperative MRI (Fig.10,11) showed that the condition became unfavorable, but the patient refused a second operation, and received the adjuvant radiotherapy and chemotherapy as the following treatments after the surgery.

Neuropathology: the histopathological examination: glioblastoma (WHO grade IV) (Fig.12-17).

The immunohistochemical analyses showed that the proliferative activity by antibodies against GFAP and Vimentin, but the anti-PCK, S-100, EMA, or CK-17 showed negative result, and the pathology was glioblastoma (WHO grade IV).

Discussion

The presence of 2 or more masses in the brain in the same patient is usually due to metastatic tumors, but glial origin tumors may also occur the similar manifestation in the brain[1]. Multicentric gliomas are considered to be quite uncommon, ranging from 1% to 10% in the various series, however the incidence rate shown in clinical, radiological, and pathological studies has been variable and uncertain[1,2]. The phenomenon of multiple gliomas was first reported by Bradley in 1880[1,3]. Subsequently Batzdorf and Malumid[4] developed a criterion for its classification, in which it was divided into 2 general types: multifocal gliomas and multicentric gliomas. Multicentric gliomas are well-separated lesions, localized in different lobes or hemispheres, without macroscopic and microscopic evidence of metastasis. Disparately, multifocal gliomas grow through dissemination via an established pathway (i.e. corpus callosum, fornix, septum pellucidum), cerebrospinal fluid channels, or the blood, or by local extension as satellite formation[1]. Glioblastoma (WHO IV) is the most common histotype of multiple gliomas, as shown in the histopathological images, however other different histotypes, such as astrocytoma, ependymoma etc, have also been reported. True multicentric glioblastoma is even rarer, with an incidence of 2.4%-4.9% of all glioblastoma reported[5]. In the 51 cases reported by Kyritsis et al, there were 31 cases of glioblastoma multiforme. The lesions of multifocal gliomas are mostly the same histotype, while multicentric gliomas may consist of several foci of the same histotype, or may be of different histotypes[6].

The pathogenesis of multicentric gliomas remains unknown. There are some hypotheses to explain multiplicity. One of the explanations is the active mutation of primitive cells with blastomatous potential, which are scattered into the nervous system during development. Or the metastasis of cells from a primary visceral tumor through the blood-brain barrier, the pathway of the metastasis in this theory is yet unknown. Willis postulated a 2-step evolution of multicentric gliomas. Firstly, neoplastic transformation may develop in the wide area or whole of the brain, and somewhere become more susceptible to neoplastic growth. Secondly, the development of neoplastic proliferation in multiple sites, come from the same or different primitive cells, with various kinds of stimulation (biochemical, hormonal, viral, parasitic disease, etc)[1,2,7,8]. Most opinions tend to the common mechanism and a style of an active migratory process, either developing within the course of the disease (metachronous) or already being present at the time of first tumor manifestation (synchronous)[9]. So far, there is no satisfactory hypothesis that clearly explains the true origin of multicentric gliomas.

There is a wide range in age at presentation of multicentric gliomas, but the majority of patients are middle aged or older, and a few child cases have also been reported[2,7,8,10]. Some child cases with multicentric gliomas are induced by radiation, sometimes appearing after therapeutic irradiation. There are 4 essential criteria for the diagnosis of radiation-induced brain tumors: *i*) tumor location within the previously irradiated field; *ii*) tumor not detected prior to the irradiation; *iii*) adequate latency period, usually more than 10 years, between irradiation and appearance of the tumor; *iv*) proven different histological types from the original neoplasm[11,12]. The clinical manifestations are various and non-characteristic, including neurological deficits, vision loss, aphasia, seizures, and intracranial hypertension, which depends on the site and extent of the lesions[2]. In this patient the clinical manifestations were intracranial hypertension, headache, nausea and visual deficits. Advanced neuroradiological techniques, such as CT, MRI, and contrast imaging, helped in discovering multiple tumors. Compared with CT scan, MRI allows for diagnosis of the features of tumor and the extent of the edemic area in terms of numeric and spatial localization. For example, some criteria have been used in distinguishing the following diseases. Metastasis tumor in brain can usually show the original visceral tumors, and the lesions are located in the infra and supratentorial cortex and white matter junction, whereas the location of multicentric gliomas are varied. The enhanced MRI of metatastatic tumors usually appears strong and different ring-shaped appearance and the multicentric gliomas have strong heterogenerous shape or a clear ring shape; the margins of the tumor are also different: the metastatic tumor with variable margins, the multicentric gliomas with indistinct margins. It is also possible that the original infection and the CSF (cerebral spinal fluid) change may help to make a diagnosis, and the diffusion-weighted imaging (DWI) can usually help in recognizing tumor necrosis (hyposignal) from an abscess (hypersignal)[2].

Another method of Dynamic Susceptibility-weighted Contrast-enhanced Perfusion MRI can be used to differentiate recurrent glioblastoma multiforme from radiation necrosis[13]. However, the diagnosis of their nature and differentiation from other pathological changes (i.e. infections, vascular, multiple lymphomas and demyelinating diseases), and the "golden standard" of diagnosis, is cerebral biopsy. Some reports[1] showed that stereotactic biopsy resulted in 0% morbidity and 0% mortality, therefore, it has been regarded as a safe and efficient method for diagnosis.

Recently, the new method, FDG-PET (positron emission tomography) has been found to provide data on the biological characteristics and proliferative capabilities of tumors' metabolism, with the special use of [18F]-fluoro-2-deoxy-D-glucose (FDG). It gives a new diagnostic perspective and potentially predicts differential metabolic patterns of progression with multiple features of tumor aggressiveness in clinic, morphology, and molecular levels[5]. The definitions and classifications for multicentric gliomas and multifocal gliomas are various，based on different authors' criteria regarding to different locations, classifications, pathological features, and prognosis of the tumor. The occurrence of true multicentric gliomas is less than which has been reported, especially in old cases far more years ago. It could be attributed to the advances in neuroradiological detection as MRI has become a routine radiological tool. Stereotactic biopsy represents a safe and satisfactory method for achieving sure diagnosis[2,14].

The prognosis of multicentric gliomas remains unfavorable, but it is emphasized that the diagnosis of multicentric rather than multiple glioma leads to a more aggressive therapy, ensuring longer survival[1,2,7]. Some authors reported that for patients with multicentric tumors, from the time of his or her first diagnosis, the median survival of the patients with metachronous MC lesions (mean survival of 353 days) was longer than that of the patients with synchronous MC lesions (mean survival of 110 days) or that of the patients without multicentricity (mean survival of 234 days)[9]. The treatment of multicentric gliomas is still controversial[15]. Current opinion ranges from rejection of surgical resection, which is a "wait and see" strategy, to the comprehensive treatments, however, some surgeons prefer the surgical removal for longer and better survival of the patients so as the following adjuvant therapies give play to more effective role when the tumor bulk is reduced. On the other hand, the opposite opinion is recommended as following. Firstly, biopsy is performed for diagnosis, and then surgery, radiotherapy and chemotherapy are followed according[16]. In this opinion, they believed that extensive resection increases the risk of haemorrhage and neurological deficit without influencing survival[7]. Concomitant chemotherapy and radiotherapy may have certain effects on glioblastoma, but they still need further trials [13,17-19]. Some authors suggest that the surgical intervention for removing the gliomas is followed by a decompressive craniotomy because sometimes the tumor cannot be completely resected[20]. The mass effect of easily accessible tumors should lead to an aggressive management, while stereotactic biopsy remains the best method for attaining histological data that decides the most suitable choice of treatment for the patients' better and longer survival[1,2,21].

Conflict of interest statement

No potential conflicts of interest were disclosed.

References

1 Maurizio S, Emanuela C, Epimenio RO, et al. Multicentric gliomas: our experience in 25 patients and critical review of the literature. Neurosurg Rev 2003; 26: 275-279.
2 Li ZH, Tian Y, Hu GZ, et al. Multiple Gliomas. Chin J Clin Oncol 2007; 4: 379-383.
3 Bradley WL. Case of gliosarcomatous tumors of the brain. Proc Conn Med Soc 1880; 2: 39-41.
4 Batzdorf U, Malumid N. The problem of multicentric gliomas. J Neurosurg 1963; 20: 122-136.
5 Cecile C, Eric G, Philippe M, et al. FDG-PET to predict different patterns of progression in multicentric glioblastomas: a case report. J Neurooncol 2008; 90: 47-51.
6 Kyritsis AP, Levin VA, Yung WK, et al. Imaging patterns of multifocal gliomas. Eur J Radiol 1993; 16: 163-170.
7 Zamponi N, Rychlicki F, Ducati A, et al. Multicentric glioma with unusual clinical presentation. Childs Nerv Syst 2001; 17: 101-105.
8 Salomao JF, Pone MV, da Silva AR, et al. Positive reactiion for cysticercosis and multicentric anaplastic oligoastrocytoma. Childs Nerv Syst 2006; 22: 182-185.
9 Hefti M, von Campe G, Schneider C, et al. Multicentric tumor manifestations of high grade gliomas: independent proliferation or hallmark of extensive disease? Cen Eur Neurosurg 2010; 71: 20-25.
10 Turola MC, Schivalocchi R, Ramponi V, et al. A rare case of multicentric synchronous bi-frontal glioma in a young female. Diagnosis and therapeutic problems: a case report. Cases J 2009; 2:81.
11 Satoshi T, Yukimasa Y, Masanori I. Pediatric multicentric glioma occurring after cranial irradiation. J Clinical Neuroscience 2009; 16: 1086-1088.
12 Kantar M, Cetingul N, Kansoy S, et al. Radiotherapy-induced secondary cranial neoplasms in children. Childs Nerv Syst 2004; 20: 46-49.
13 Sridhar T, Gore A, Boiangiu I, et al. Concomitant (without adjuvant) temozolomide and radiation to treat glioblastoma: a retrospective study. Clin Oncol (R Coll Radiol) 2009; 21: 19-22.
14 Synowitz M, von Eckardstein K, Brauer C, et al. Case history: multicentric glioma with involvement of the optic chiasm. Clin Neurol Neurosurg 2002; 105: 66-68.
15 Francesco V, Marc S, Hugues D. Combined multiple surgical intervention and chemotherapy for multicentric WHO grade II glioma. Acta Neurochir 2009; 151: 1699-1704.
16 Takashi S, Patricia A, John M, et al. Papillary tumor of the pineal region: report of a rapidly progressive tumor with possible multicentric origin. Pediatr Radiol 2009; 39: 188-190.

17 Raizer JJ, Abrey LE, Lassman AB, et al. A phase II trial of erlotinib in patients with recurrent malignant gliomas and nonprogressive glioblastoma multiforme postradiation therapy. Neuro Oncol 2010; 12: 95–103.
18 Raizer JJ, Abrey LE, Lassman AB, et al. A phase I trial of erlotinib in patients with nonprogressive glioblastoma multiforme postradiation therapy, and recurrent malignant gliomas and meningiomas. Neuro Oncol 2010; 12: 87–94.
19 Dwarakanath BS, Singh D, Banerji AK, et al. Clinical studies for improving radiotherapy with 2-deoxy-D-glucose: present status and future prospects. J Cancer Res Ther 2009; 5: S21–26.
20 Wang ZC. Neurosurgery. Wuhan: Hubei Science Publishing House 2005; 430 (Chinese).
21 Vergani F, Sanson M, Duffau H. Combined multiple surgical intervention and chemotherapy for multicentric WHO grade II glioma. Acta Neurochir (Wien) 2009; May 5 [Epub ahead of print].