Clinical Case Report

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Multiple cerebral gliomas mimicking central nervous system inflammatory demyelinating diseases

A rare case with review of literature

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Abstract

Rationale: Multiple cerebral gliomas (MCGs), usually classified into multifocal and multicentric subtypes, represent major diagnostic challenges as their clinical, radiologic, and pathohistological features are not uniform, often mimicking brain metastatic tumors or central nervous system inflammatory demyelinating diseases (IDD).

Patient concerns: Here, we report a rare case of MCGs with isolated seizures and 4 lesions in the brain, that was initially misdiagnosed as IDD during treatment.

Diagnosis: The pathological diagnosis was astrocytoma, which was classified as a World Health Organization grade II glioma.

Interventions: The patient was treated with dexamethasone and sodium valproate when he was misdiagnosed as having IDD. After the pathological diagnosis was obtained, he was treated with temozolomide and radiotherapy.

Outcomes: Three months after the above treatment, the health of the patient had improved; he was asymptomatic, and presented with better radiological manifestations.

Lessons: Diagnostic imaging is valuable in differential diagnosis. Magnetic resonance spectroscopy is a promising technique for the assessment and characterization of lesions, though its role in definitive diagnosis is not yet defined. Brain tissue biopsy remains the golden standard for definitive diagnosis. In China, for various reasons, craniotomy biopsy is not performed routinely in patients with multiple intracranial lesions, and stereotactic cranial biopsy may be a more viable option because of its safety and cost-effectiveness. In summary, this case demonstrates that MCGs need to be included in the differential diagnosis of unknown intracranial multiple lesions.

Abbreviations: ADEM = acute disseminated encephalomyelitis, ANCA = antineutrophil cytoplasmic antibodies, Cho/NAA = choline/N-acetyl-aspartate, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, DWI = diffusion weighted imaging, GFAP = glial fibrillary acidic protein, HBV = hepatitis B virus, HCV = hepatitis C virus, HE = hematoxylin-eosin, HIV = human immunodeficiency virus, IDD = inflammatory demyelinating diseases, MCGs = multiple cerebral gliomas, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, MS = multiple sclerosis, T1WI = T1-weighted image, T2WI = T2-weighted image, TIDD = tumor-like inflammatory demyelinating diseases, WHO = world health organization.

Keywords: astrocytoma, brain neoplasms, demyelinating diseases, diagnosis, differential

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1. Introduction

Multiple cerebral gliomas (MCGs) are among the uncommon causes of intracranial multiple lesions and may present a diagnostic challenge to physicians, often mimicking several other diseases of the central nervous system (CNS) clinically and radiologically. Among those diseases prone to be misdiagnosed as MCGs, CNS inflammatory demyelinating diseases (IDDs) including multiple sclerosis (MS) are not very often reported. Notably, the clinical manifestations of MCGs are variable and noncharacteristic, such as neurological focal signs and seizures,[1,2] which are also observed in IDD.[3] For radiological diagnosis of multiple lesions in the brain, magnetic resonance imaging (MRI) using contrast-enhancing agents, a powerful imaging technique, is the technique of choice. However, it is still a challenge to distinguish between MCGs and IDD by morphological changes alone. Although magnetic resonance spectroscopy (MRS) has the advantage of distributing chemical metabolites within the region of interest to differentiate gliomas from nonneoplastic conditions,[4] a biopsy is still the golden standard for final diagnosis.[5] In this article, we report a rare case of

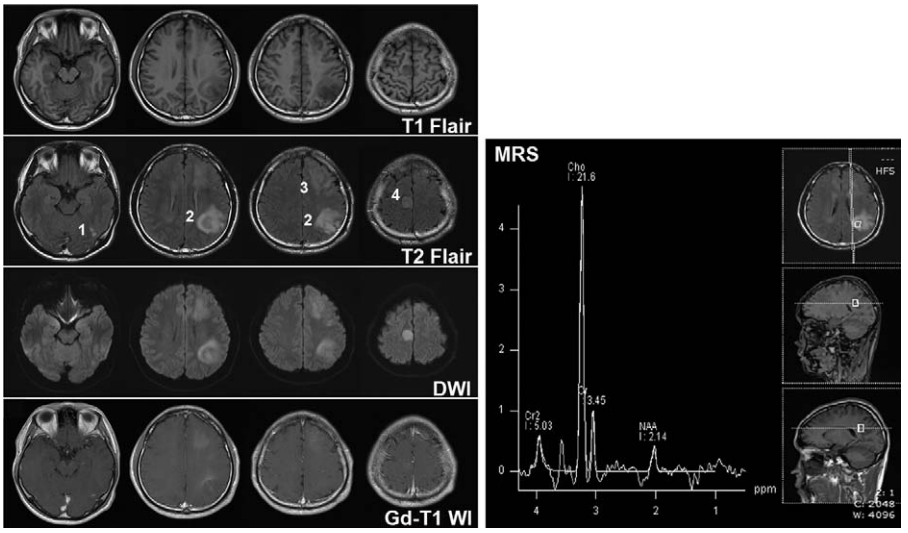

Figure 1. Head MRI and enhancing scanning demonstrated 4 lesions, 1 each in the left temporal (1), frontal (3), and temporal-parietal (2) lobes, and in the right paramedian frontal lobe beneath the cortex (4). These lesions had low signals in T1WIs and high signals in T2WIs and DWI without obvious edema and mass effect. Three lesions were partially enhanced with gadolinium dimeglumine, whereas the lesion in the right paramedian frontal lobe beneath the cortex did not show such an enhancement. An elevated Cho/NAA ratio was examined using MRS in regions with lesions. Cho = choline; DWI = diffusion weighted imaging; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NAA = N-acetyl-aspartate; T1WI = T1-weighted image; T2WI = T2-weighted image.

MCGs, which mimicked IDD once during treatment. We present a summary of the case, focusing on the differentiation between MCGs and IDD. Furthermore, we present a review of related literature.

2. Case presentation

A previously healthy 38-year-old Chinese man presented with a seizure for about 3 minutes when he was at dinner. After the seizure, he woke up and felt normal, so he visited the hospital 3 days later. He had a history of smoking 10 cigarettes a day for the past 12 years and his brother had a history of epilepsy. Neurological examination of the patient was normal and laboratory investigation results were notable for leukocyte counts (16.74×10^9/L [85.3% neutrophils]). Head MRI and enhancing scanning demonstrated 4 lesions in the left temporal, frontal, temporal-parietal lobes, and in the right paramedian frontal lobe beneath the cortex. These lesions had low signals on T1-weighted images (T1WI) and high signals on T2-weighted images (T2WI). Three lesions were partially enhanced with gadolinium dimeglumine, whereas the lesion in the right paramedian frontal lobe beneath the cortex did not show such an enhancement. Physicians at the hospital the patient had visited were unclear about the definite diagnosis, and the patient was transferred to our hospital. Careful neurological examination showed a left Babinski sign positive status. Extensive laboratory and investigative workup revealed elevated homocysteine (18 μmol/L) and carbohydrate antigen 72-4 (27.04 U/mL) levels, whereas the following results were within normal limits: erythrocyte sedimentation rate, thyroid-stimulating hormone, free T3, free T4, antithyroid peroxidase antibody, antinuclear antibody, antineutrophil cytoplasmic antibodies panel, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, syphilis, anti-Hu, anti-Yo, anti-Ri, anti-aquaporin-4/neuromyelitis optica-immunoglobulin G (IgG), anti-myelin oligodendrocyte glycoprotein-IgG, anti-myelin basic protein-IgG, anti-*N*-methyl-D-aspartic acid receptor-IgG, anti-amino-3-hydroxy-5-methylisoxazole-4-propionicacid receptor-IgG, anti-Leucine glioma inactivating protein 1 receptor-IgG, anti-contactin-associated protein 2 receptor-IgG, anti-γ-aminobutyricacid B receptor-IgG and white blood cell count, and protein and intrathecal synthesis of oligoclonal bands of lumbar puncture. Computed tomography (CT) of the lungs revealed a minor infection. Finally, the head MRI scans obtained at the earlier hospital were sent to an experienced neuroradiologist, who gave a tentative diagnosis of IDD. The patient was then treated with dexamethasone (10 mg/d), and sodium valproate (1.0 g/d) for 2 weeks, and discharged with no neurologic deficit.

About 2 months after the first seizure, the patient experienced a second seizure when he was tired. This episode was associated with urinary incontinence and was thus more severe than the earlier episode. Two weeks later, he experienced frequent seizures and was transferred to our hospital again. Neurological examination showed mild left leg weakness with no abnormalities of cranial nerves and sensation. Head MRI, including enhancing scanning and diffusion weighted imaging (DWI), and MRS were performed for the second time, in which the size of the multiple lesions was similar to that observed earlier, whereas DWI showed higher signal intensity. An elevated choline/N-acetyl-aspartate (Cho/NAA) ratio was detected in the lesion regions by MRS (Fig. 1). Expert neurologists and radiologists were consulted and were of the collective opinion that the clinical and radiologic manifestations of the patient were highly suggestive of IDD, and a tumor should be a differential diagnosis considering MRS findings. To obtain a definitive diagnosis, a brain tissue biopsy was considered as necessary, though the patient did not consent to the biopsy procedure. As per the most probable diagnosis, he accepted the treatment for IDD, and was treated with methylprednisolone pulse therapy (1000 mg of intravenous methylprednisolone/d for 5 days), followed by oral corticosteroid administration. Sodium valproate was used as earlier, and oxcarbazepine (600 mg/d) was added as an antiepileptic drug.

During the above treatment, the patient recovered well and no more seizures occurred. After more than a month, he had frequent seizures again and was sent to the emergency department, where cranial CT was performed and showed errhysis of the lesion in the left parietal lobe (see Supplemental

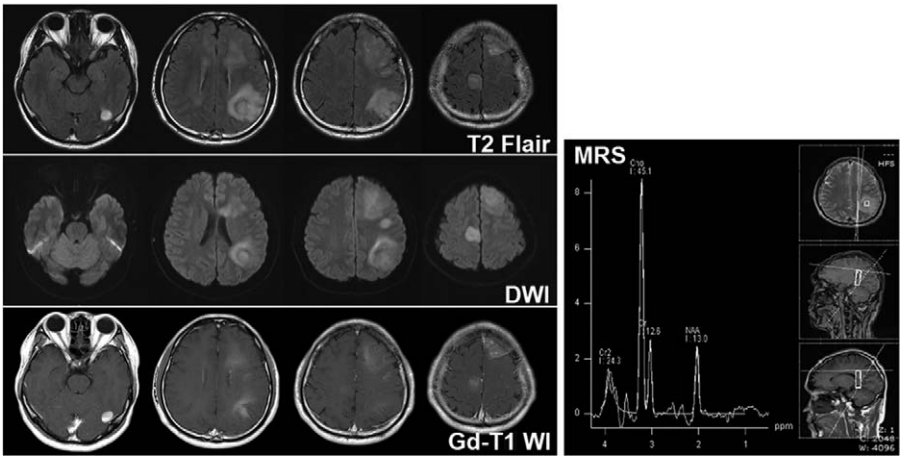

Figure 2. Head MRI and enhancing scanning showed that all the 4 lesions were larger in size compared with those in Figure 3. The lesions showed more obvious enhancement, and the lesion in the right paramedian frontal lobe beneath the cortex, which was not enhanced in Figure 3, showed significant enhancement. Cho = choline; DWI = diffusion weighted imaging; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NAA = N-acetyl-aspartate; T1WI = T1-weighted image.

Figure 1, http://links.lww.com/MD/C52, which demonstrated that the lesions were more likely malignant). Head MRI, enhancing scanning, DWI, and MRS were also performed and showed that the lesions had increased in size compared to earlier (Fig. 2). At this time, the patient agreed to the biopsy procedure, and a stereotactic biopsy was obtained. The pathological diagnosis was astrocytoma, which was classified as a World Health Organization (WHO) grade II glioma. Hematoxylin-eosin-stained paraffin wax sections showed enlarged tumor cells and enhancement of chromatin in most nuclei, and several areas in the lesion revealed pink-stained cytoplasm, neuritis, and nuclear polymorphism. Immunohistochemistry with anti-Ki67 (a marker of cell proliferation) showed a high proliferation index and antiglial fibrillary acidic protein was positive (Fig. 3). Nestin, Olig, and S-100 were also positive (see Supplemental Figure 2, http://links.lww.com/MD/C52, with evidence of an aggressive malignant astrocytoma). The patient was treated with temozolomide (150 mg/m^2) and radiotherapy. In the next 3 months, his health had improved, and he presented with better radiological manifestations (Fig. 4). None of the prior symptoms had reappeared, and he was placed on a follow-up schedule.

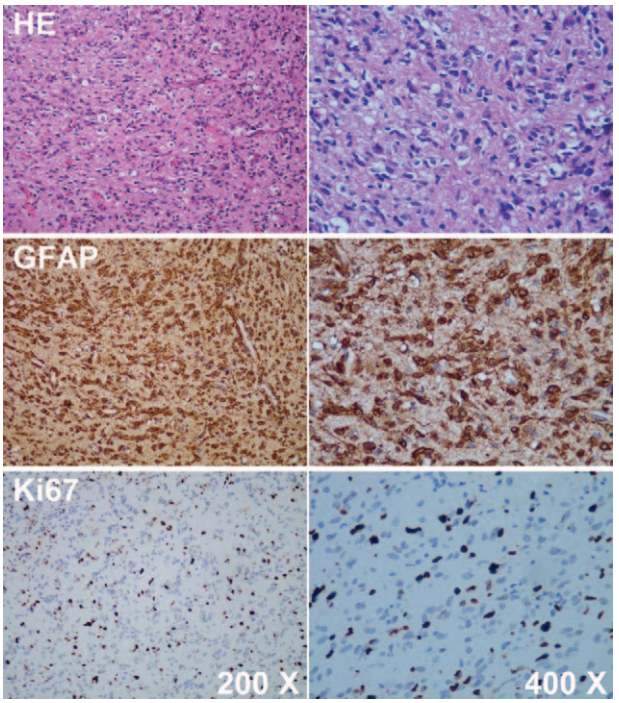

Figure 3. Immunohistochemical examination images. GFAP and Ki67 were positive. GFAP = glial fibrillary acidic protein; HE = hematoxylin-eosin.

3. Discussion

The presence of 2 or more cerebral masses in the brain region usually presents a diagnostic challenge to physicians. The most commonly considered causes are vascular diseases, encephalopyosis, necrosis, demyelinating diseases, or tumors (including metastatic disease, multiple lymphomas, and MCGs). Among

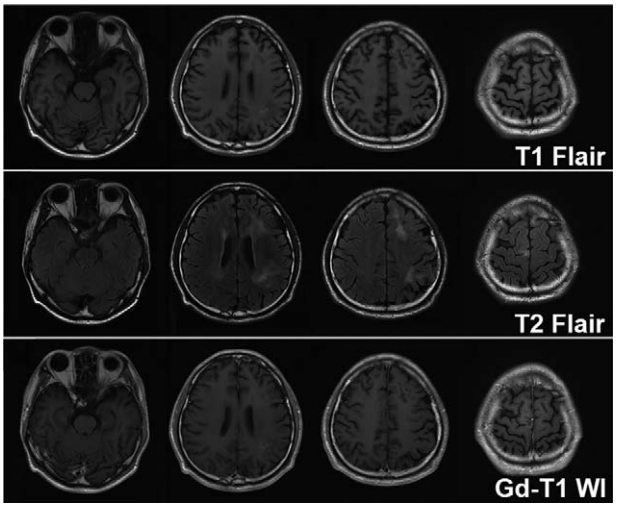

Figure 4. Head MRI and enhancing scanning images obtained 3 months after treatment with temozolomide. The lesions were much smaller compared with those in Figure 4, with little enhancement. The lesion in the left temporal had disappeared. MRI = magnetic resonance imaging.

these, the differential diagnosis between demyelinating diseases and tumors is the most confusing. Though metastatic disease is highly prevalent among CNS tumors, the clinical and radiological manifestations of MCGs are frequently mistaken for those of IDD, especially when no primary tumor is detected and related history is absent.

MCGs, described by Gower in 1896 for the first time, are rare and poorly documented. Their incidence ranges from 0.5% to 20% among all patients with gliomas.[6,7] There are 2 methods of classification of MCGs. According to the location of the lesions, MCGs are classified into multifocal and multicentric gliomas.[8] Multifocal glioma lesions originate from the first lesion and disseminate or grow along an established route, spread via nerve fiber bundles (corpus callosum, fornix, and septum pellucidum), cerebrospinal fluid (CSF), or the blood channels, or locally extend through satellite formation. Multicentric gliomas may also be widely separated in different lobes or hemispheres through unknown channels, without any macroscopic and microscopic evidence of metastasis.[2] According to the timeline of lesion occurrence, MCGs are divided into synchronous (lesions occur at the same time) and metachronous (lesions occur months or years apart) types[9] (Fig. 5). However, the above definitions are on the basis of pathology and are difficult to distinguish by radiological imaging. Given that the biopsy procedure is not accepted routinely and widely in the Chinese population because of lack of education, the classification into early (lesions occurring prior to treatment) and late (lesions occurring during or after treatment) stage lesions[2] is more convenient and helpful for clinical application. In addition, distinguishing between multicentric and multifocal gliomas is not of clinical value, as the prognosis of patients with MCGs is generally poor regardless of subtype.[10]

Although first reported more than a century ago, the pathogenesis of MCGs remains unclear. It is thought that MCGs may develop over 2 stages. In the first stage, known as neoplastic transformation or initiation, a large portion of the brain is thought to become more susceptible to neoplastic growth. In the second stage, known as promotion, neoplastic proliferation occurs at multiple sites induced by stimulants of various origins (hormonal, biochemical, or even viral)[11,12] (Fig. 6).

MCGs mainly occur in people of middle or old age and the number of male patients is slightly higher than that of female patients, though no significant differences have been found.[13] The clinical manifestations of MCGs are variable and non-characteristic. The most common manifestations are neurological focal signs and intracranial hypertension, and epilepsy and seizures may also be observed.[1,2] The above clinical characterization is true of IDD. Some IDD patients, similar to those with MCGs, may present isolated neurological focal signs or seizures,[14,15] especially in the absence of history of demyelinating episodes. Thus, it is difficult to distinguish these 2 diseases based solely on differences in clinical manifestations. In the present case, the initial misdiagnosis of IDD may be attributed to isolated clinical symptoms (only seizures), no evidence of neoplastic diseases, and radiographic findings. Because of the lower morbidity of MCGs compared to that of IDD, the diagnosis of IDD is usually considered prior to MCGs, which thus leads to under treatment.

IDD of the CNS are a series of diseases, including MS, acute disseminated encephalomyelitis, and tumor-like inflammatory demyelinating diseases, which are easily mistaken for MCGs.[16] Imaging is a valuable diagnostic method to distinguish between these disease types and arrive at a definitive diagnosis.[17] The MCG lesions were 90% hypointense to isointense on T1WI, and

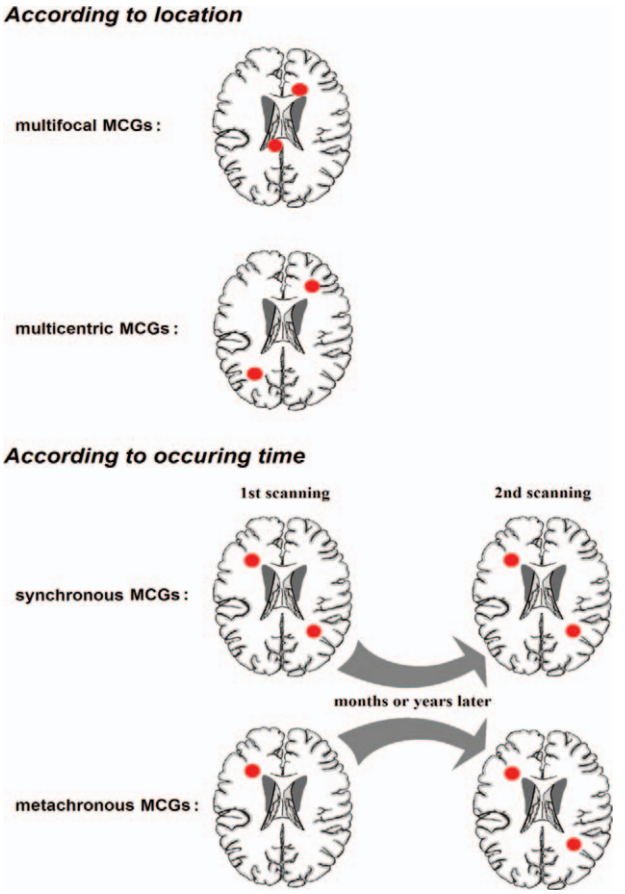

Figure 5. Classification of MCGs. MCGs = multiple cerebral gliomas.

were all hyperintense on T2WI. After using contrast-enhancing agents, approximately 85% of the lesions demonstrated a moderate to strong enhancement, most of which was heterogeneous or ring shaped, and rarely homogeneous. More than 70% of lesions were accompanied by moderate to serious edema and mass effect. The MR feature of each lesion even in the same patient may be different, which increases the difficulty of diagnosis. The lesions of IDD are hypointense on T1WI and hyperintense on T2WI with little to mild edema and mass effect, with heterogeneous or open ring-shaped enhancement.[18,19,20] In the present case, the edema and mass effect of the MR lesions were not obvious from beginning to end, and there was mild enhancement in the lesions of the left temporal, frontal, and parietal lobes No enhancement was observed in the lesions of the right paramedian frontal lobe beneath the cortex in the first 3 MRI scans (Fig. 1), which were

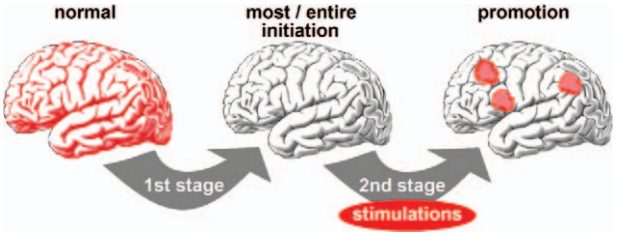

Figure 6. The possible pathogenesis of MCGs. MCGs = multiple cerebral gliomas.

Table 1

MR image features of MCGs, MS, TIDD, and ADEM.

Image Features	MCGs	TIDD	MS	ADEM
Location	Common: parietal, frontal, temporal lobe Uncommon: thalamus, brain stem, occipital lobe, spinal cord	Supra- and/or subtentorial, junction of white and grey matter	Supra- and/or subtentorial, typically periventricular white matter	Supra- and/or subtentorial white and grey matter
Size and shape	Often different	>2.0 cm	<1.0 cm; circular or ovoid plaques	Often different and obscure boundary
Density	T1: hypo- to isointense mostly T2: all hyperintense	T1: hypointense T2: hyperintense	T1: hypointense T2: hyperintense	T1: hypointense T2: hyperintense
Edema and mass effect	Moderate to serious in majority absent in minority	Proportionally minor relative to plaque size	Absent	Mild edema and necrosis in the central of lesions
Enhancement	Usually strong and rarely homogeneous	Incomplete or open-ring shape	Coexistence of enhanced and nonenhanced plaques	Strong and heterogeneous
MRS	Elevated Cho/NAA	Decreased NAA peak and slight elevated Cho level	Decreased NAA peak and elevated Cho level	Decreased NAA peak and normal Cho level

ADEM = acute disseminated encephalomyelitis, Cho/NAA = choline/N-acetyl-aspartate, MCGs = multiple cerebral gliomas, MS = multiple sclerosis, TIDD = tumor-like inflammatory demyelinating diseases.

more likely IDD than MCGs. In the present case, all of the above mentioned factors may have led to misdiagnosis at the first visit to our hospital. Table 1 shows the differential MRI characteristics among the above mentioned diseases.

MRS is a promising technique for the assessment and characterization of multiple lesions in the brain. When the patient was first transferred to our hospital, in addition to reviewing the prior MRI and enhancing scans, MRS was performed for differential diagnosis. The results of MRS showed a significant increase of the Cho peak reflecting gliocyte proliferation and a decrease in the NAA peak reflecting neuronal destruction and axonal damage. Although the elevated Cho/NAA ratio on the MRS suggested that the lesions were more likely malignant, the diagnosis of IDD was not totally excluded. An increased Cho/NAA ratio on MRS is also usually seen in tumefactive demyelinating lesions.[21,22,23] Owing to the similarity in the increase of Cho peak and decrease of NAA peak between MCGs and IDD, MRS may not allow for a definitive differential diagnosis. Moreover, its role in diagnosis has not yet been standardized because of lack of standardized research data comparing the relevant diseases.

Under such circumstances, the final diagnosis may rely heavily on histopathological examination, including surgical and stereotactic biopsies. Stereotactic biopsy offers several advantages for the pathological diagnosis of MCGs, as it circumvents the need for trepanation, provides easy access with negligible brain damage, and allows for precisely locating areas of interest. When gliomas are large and have a marked mass effect, surgical biopsy may be a better choice for clinical diagnosis and concurrent treatment. However, surgical treatment of MCGs remains controversial (from more aggressive gross total resection to rejection of surgical treatment),[24,25] which leads to limited application of surgical biopsy clinically. Therefore, stereotactic biopsy represents a safe and satisfactory method for pathological diagnosis of MCGs. In the present case, because of the patient's refusal to undergo biopsy and the diagnostic ambiguity at the clinicians' end, the patient initially accepted methylprednisolone pulse therapy followed by a MR examination. However, he was hospitalized for the third time and received a stereotactic biopsy (the pathologic diagnosis was astrocytoma, WHO grade II). Most MCGs can be classified as glioblastoma (WHO grade IV) pathologically. In addition, anaplastic astrocytoma, anaplastic oligoastrocytoma, gliosarcoma, oligoastrocytoma, and ependymoma have also been reported in MCGs.[26–29] MCGs have a worse prognosis than do solitary tumors and the survival time ranges from 2 to 10 months under treatment, including radio-, chemo-, and immunotherapies.

There remain 2 problems to be further considered. First, several biochemical markers of CSF including the white blood cell count, protein, and intrathecal synthesis of oligoclonal bands were negative in this case. Although positive oligoclonal band status is an authenticating characterization of IDD, a negative status is observed in most IDD cases. The CSF manifestations of MCGs have been infrequently reported. Second, the biopsy tissue was obtained only from the lesion in the left frontal lobe in this case. However, the histotype of all the 4 lesions may have been different, and it is possible that multiple sclerosis and glioblastoma may have cooccurred, as reported previously.[30,31]

4. Conclusion

It is difficult to diagnose MCGs of the brain without histopathological examination. Herein, we report an uncommon case of MCGs with a total of 4 lesions in the hemispheres, associated with uncommon symptoms such as epilepsy. MCGs are easily misdiagnosed as CNS IDDs and metastatic diseases according to radiological findings as in our case. In line with MRI and enhancing scanning, MRS adds more biochemical and molecular information and is helpful for accurate diagnosis. If multiple lesions are present at various locations in the hemispheres, a diagnosis of MCGs needs to be evaluated. In such cases, stereotactic intracranial biopsy is recommended for differential diagnosis.

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