Early Appearance of High Grade Glioma on Magnetic Resonance Imaging

Noriyuki NISHI, Shozo KAWAI*, Taiji YONEZAWA, Kenta FUJIMOTO*, and Katsuya MASUI*

Department of Neurosurgery, Nara Prefectural Mimuro Hospital, Nara; *Department of Neurosurgery, Osaka General Medical Center, Osaka

Abstract

The early appearance of high grade glioma on magnetic resonance (MR) imaging was retrospectively reviewed in the clinical records and MR images of 52 patients with intracerebral glioma treated in Osaka General Medical Center between 1997 and 2006. Three patients had no abnormal findings, and four patients had only hyperintense areas on T2-weighted imaging at initial MR examination. Five of the seven patients presented with generalized seizures. Six of the seven patients developed tumor progression within only 5 months. All patients underwent surgical tumor resection and the histological diagnoses were all high grade gliomas, glioblastomas in five, gliosarcoma in one, and anaplastic astrocytoma in one. Surveillance MR imaging should be performed at short intervals in adult patients presenting with seizures but with no or minimal abnormalities on initial MR imaging to identify progression of high grade glioma at the earliest opportunity.

Key words: high grade glioma, early appearance, magnetic resonance imaging, seizure

Introduction

Early diagnosis of high grade glioma is important to achieve the optimum outcome for the patient. Any delay in correct diagnosis is considered to lead to poor outcome. Computed tomography (CT) has failed to detect glioma at initial and later examinations. The introduction of magnetic resonance (MR) imaging has greatly improved the detection of intracranial lesions and apparently solved the difficulty with the diagnosis of glioma. However, neurosurgeons, neurologists, and neuroradiologists still encounter patients with high grade gliomas who present with no or minimal abnormalities on initial MR imaging.

This study retrospectively reviewed the clinical records and MR imaging findings in patients with intracerebral glioma to characterize the early MR imaging appearance of high grade glioma.

Clinical Material and Methods

A total of 52 consecutive patients with intracerebral gliomas were treated in Osaka General Medical Center between January 1997 and December 2006. MR imaging was performed using a 1.5-T Signa Advantage (GE Medical Systems, Milwaukee, Wis., U.S.A.) until January 2003 and a 1.5T Intra Master (Philips Medical Systems, Eindhoven, the Netherlands) from February 2003. Patients who underwent only CT were excluded. Seven patients, four men and three women aged from 50 to 70 years (mean 62.7 years), showed no or minimal abnormalities on initial MR imaging, whereas the others demonstrated the typical findings of high grade gliomas, such as heterogeneous enhancement and mass effect.

The clinical records and the neuroimaging findings of the seven patients were retrospectively reviewed to investigate the initial symptoms, initial MR imaging features, time to recognition of progression, location of the tumors, and histological diagnosis. All patients underwent at least T1-weighted, T2-weighted, and fluid-attenuated inversion recovery imaging. Four of the seven patients also underwent MR imaging with gadolinium. The patients presenting with seizure underwent electroencephalography (EEG). Whole brain radiation or extensive local irradiation (50–60 Gy) was administered to six patients. Case 6 developed brain edema at the beginning, so radiotherapy was abandoned. Three patients received chemotherapy using ni-
Table 1 Clinical, histological, and magnetic resonance (MR) imaging features of cases of occult glioma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Initial symptom</th>
<th>Initial MR imaging features</th>
<th>Time to recognition of progression (mos)</th>
<th>Location</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>seizure</td>
<td>normal</td>
<td>3</td>
<td>lt temporal</td>
<td>glioblastoma</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>seizure</td>
<td>normal</td>
<td>5</td>
<td>lt frontal</td>
<td>glioblastoma</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>dizziness</td>
<td>$T_2$ hyperintense area</td>
<td>24</td>
<td>rt frontal</td>
<td>anaplastic astrocytoma</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>seizure</td>
<td>normal</td>
<td>3</td>
<td>lt temporal</td>
<td>glioblastoma</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>dizziness</td>
<td>$T_2$ hyperintense area</td>
<td>4</td>
<td>lt temporal</td>
<td>glioblastoma</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>seizure</td>
<td>$T_2$ hyperintense area</td>
<td>3</td>
<td>lt temporal</td>
<td>gliosarcoma</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>seizure</td>
<td>$T_2$ hyperintense area</td>
<td>3</td>
<td>lt frontal</td>
<td>glioblastoma</td>
</tr>
</tbody>
</table>

mustine hydrochloride. All patients died of tumor progression.

**Results**

Table 1 summarizes the clinical, histological, and MR imaging features. Five of the seven patients presented with seizures as the initial symptom and had no history of seizures. EEG findings on admission were normal. The other two patients underwent MR imaging for examination of dizziness, but the initial symptoms were considered to be unrelated to the brain tumors.

Initial MR imagnings found no abnormalities in three patients, and minimal abnormalities in four patients consisting of hyperintense areas on $T_2$-weighted imaging, which were misinterpreted as ischemic lesions, in contrast to the typical findings of malignancy such as gadolinium enhancement and mass effect. The overall findings of physical and neurological examinations, EEG, and other neurological imaging were normal in the seven patients, so were interpreted as non-neoplastic and the patients were discharged within a few days.

Six of the seven patients developed tumor progression within only 5 months. Four of the tumors were located in the left temporal lobe, two in the left frontal lobe, and one in the right frontal lobe, so mainly occurred in the functionally dominant left cerebral hemispheres. All patients underwent surgical tumor resection. The histological diagnoses were glioblastoma in five patients, gliosarcoma in one, and anaplastic astrocytoma in one. No patient had low grade glioma.

**Illustrative Cases**

**Case 1:** A 68-year-old man, who did not have any history of epilepsy, suffered generalized tonic seizure on February 3, 1998. He was admitted to our institute for further examinations 10 days later. Physical examination, blood examination, CT, and EEG found no abnormalities. MR imaging showed no abnormalities in the central nervous system (Fig. 1). No definite focal lesion was identified, so he was
Case 4: A 53-year-old man suffered generalized seizure on November 16, 2000 and was transferred to our institute for further examination on the next day. Neurological and physical examinations, EEG, and MR imaging found no abnormalities, so he was discharged and followed up as an outpatient.

T2-weighted MR imaging revealed a hyperintense area and constriction of the sulci in the left temporal lobe on February 28, 2001 (Fig. 3), despite the absence of symptoms and normal neurological findings. Positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) revealed focal increases of uptake in the left temporal lobe. The left temporal lesion was considered to be brain tumor rather than ischemic or degenerative disease. We recommended surgical management including biopsy, but he refused informed consent so we followed him up as an outpatient.

He was admitted to our institute with severe headache and sensory aphasia on July 5, 2001. MR imaging revealed a heterogeneously enhanced tumor in the temporal lobe (Fig. 4). He underwent subtotal removal of the tumor on July 12, 2001. The histological diagnosis was glioblastoma. He was treated with whole brain radiation therapy and discharged. He died of recurrence of glioblastoma on November 13, 2001.

**Discussion**

In our series, many patients with high grade gliomas had the typical MR imaging findings of high grade gliomas including glioblastoma which appear as prominent heterogeneous intensity on T2-weighted images, with marked and irregular enhancement with gadolinium. Only seven patients presented with symptoms before showing such typical MR imaging features. Experience of false-negative detection of glioma by CT indicates that important factors include small tumor size and low cell density, isodense tumor mass, absence of acquired changes in the blood-brain barrier, and poor scan resolution. We suggest that MR imaging may fail to detect gliomas due to similar factors.

The early appearance of high grade gliomas on MR imaging may manifest as minimally abnormal small hyperintense areas on T2-weighted imaging which might be misinterpreted as ischemic change. MR imaging detects malignant changes only several months later. Similarly, initial MR imaging showed no or minimal abnormalities, whereas subsequent MR imaging revealed high grade gliomas within a short time in our seven patients.

Five of our seven patients presented with seizure as the initial symptoms. Three authors have reported patients with negative findings on initial CT or MR imaging who all later presented with seizures, eight of nine patients with negative findings on MR imaging presented with seizures, and five of eight patients presented with only seizures, indicating that seizures are the most sensitive clinical indicator.
of glioma.\textsuperscript{13} Study of epileptogenic areas removed from patients with negative findings on MR imaging identified small tumor-like nodules in the temporal lobe.\textsuperscript{5} Some of these nodules showed early histological evidence of neoplastic transformation, suggesting possible involvement as the origins for the further development of glioma. Six of our seven patients had high grade glioma in the left cerebral hemisphere, four of which were in the left temporal lobe. The present study suggests that high grade glioma in the left temporal lobe, even if very small or undetectable, may manifest as seizure or similar symptoms. Accordingly, we suggest that seizure should be considered as an indicator of occult high grade glioma. Adult patients who present with seizure but with no or minimal abnormalities on MR imaging should possibly be scheduled for follow-up MR imaging.

MR imaging findings changed from negative to positive within 3 to 5 months, except in Case 3 within 24 months, and indicated high grade gliomas. Many patients have developed CT or MR imaging changes within 6 months,\textsuperscript{4,8,9,11,15,18,20} and rapid follow-up CT or MR imaging is recommended.\textsuperscript{11,12,20} However, the interval of surveillance CT or MR imaging is unclear. Many patients presented with malignant progression within 5–6 months, so we recommend that surveillance MR imaging be performed a few times in the initial 6 months.

Small gliomas are histologically benign,\textsuperscript{17} but the patients may develop high grade gliomas later with poor outcome, even if initial CT and/or MR imaging findings were negative.\textsuperscript{4,8,9,11,13–15,18,20} Similarly, all of our patients developed high grade gliomas. The origin of malignant tumor cells in the brain is unknown, and the initiation of high grade glioma needs further investigation.

More sensitive tools and methods than usual imaging may be necessary to identify neoplasm or non-neoplasm in the early stages. Diffusion-weighted MR imaging is suitable for the early diagnosis of malignant glioma.\textsuperscript{1,10} No cases were examined by diffusion-weighted MR imaging in our seven patients. The findings of diffusion-weighted MR imaging will be very interesting. Technetium-99m scintigraphy\textsuperscript{7} and transcranial sonography\textsuperscript{22} may be useful, and FDG-PET has received much attention.\textsuperscript{3,6,16,19} FDG-PET revealed that the hyperintense area on T2-weighted imaging was neoplasm in Case 4, so we consider FDG-PET is very valuable for the diagnosis of brain neoplasm. In the future, FDG-PET may facilitate the diagnosis of brain neoplasms in patients with normal findings on initial MR imaging.

The present study of patients with gliomas not identified by initial MR imaging showed that such gliomas are characterized by initial manifestation as seizure, possibly related to the most common location in the left temporal lobe, short interval of only 5 months before tumor progression, and high likelihood of malignant progression. Surveillance MR imaging should be continued at short intervals in adult patients presenting with seizure and normal or minimally abnormal findings on initial MR imaging to identify and begin treatment of high grade glioma at the earliest opportunity.

References

12) Massry GG, Morgan CF, Chung SM: Evidence of optic pathway gliomas after previously negative neuro-


Address reprint requests to: Noriyuki Nishi, M.D., Department of Neurosurgery, Nara Prefectural Mimuro Hospital, 1–14–16 Mimuro, Sango-cho, Ikoma-gun, Nara 636–0802, Japan.

Commentary

It is important to make an early diagnosis of high-grade glioma for the good prognosis of patients. Up to now, MR imaging has remained the golden standard to identify these tumors. The authors did a good job to review the early appearance of high grade glioma on MR imaging of 7 patients with clinical records. They suggested that it was important to perform surveillance MR imaging at short intervals in adult patients with clinical presentations with no or minimal abnormalities on initial MR imaging. I think the prognosis of early diagnosed patients with maximal safe tumor resection will be better. Please follow up the 7 patients. Advanced neuroimaging study, especially different sequences of MR imaging, is encouraged.

Dapeng Mo, M.D.
Department of Neurosurgery
Peking University First Hospital
Beijing, P.R.C.