[SpringerLink] DOI 10.1007/s11805-007-0379-y

Multiple Gliomas

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This work was supported by grants from the National Science Foundation of China (No. 30672159) and the New Century Excellent Talents in Chinese Universities (No.NCET-06-0306)

Received September 24, 2007; accepted November 27, 2007.

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ABSTRACT Multiple gliomas are well-recognized but uncommon tumors. The incidence of multiple gliomas according to some reports ranges from 0.5% to 20% of all gliomas diagnosed. Multiple gliomas can be divided into two categories. One is by location of the lesions (multifocal and multicentric). The second type is by the time of the lesions occur (synchronous and metachronous). The lesions generally show hypo, or isodensity on CT; a hypo- or isointense signal on T1-weighted images, and a hyperintense signal on T2-weighted images. Glioblastoma is the most frequent histotype. The prognosis of multiple gliomas remains unfavorable. The treatment of multiple gliomas includes surgery, radiotherapy and chemotherapy. Distinction between multicentric and multifocal gliomas is difficult. This report reviews in detail the aspects of multiple gliomas mentioned above.

KEYWORDS: multiple glioma, diagnosis, MRI, pathology, treatment.

The presence of two or more cerebral masses in the same individual is usually due to metastactic disease. However, this can also be encountered in brain tumors of glial origin. Multiple gliomas are well-recognized but uncommon tumors. Multiple gliomas were described by Gower in 1896 for the first time[1]. The incidence of multiple gliomas is variable, ranging from 0.5% to 20% of all gliomas diagnosed in various reports. However, in most series, it was described as ranging from 2.5% to 5%[2-4]. Barnard and Geddes[5] studied a series of 241 gliomas, from which they found 35 cases (14.5%) of multiple gliomas. Kyritsis et al.[6] reported 51 multiple glioma patients extracted from a large group of 554 consecutive patients with primary cerebral gliomas (9.2%).

Classification

Multiple gliomas can be classified into two general types. The first is by location of the lesions.These can be sub-diveded into multifocal and multicentric gliomas. Multifocal gliomas grow through dissemination along an established route, spreading through commissural pathways (corpus callosum, fornix, septum pellucidum), cerebrospinal fluid (CSF) channels, or the blood, or by local extension through satellite formation. In contrast, multicentric gliomas are widely separated lesions in different lobes or hemispheres that can not be attributed to any of the above pathways, without macroscopic and microscopic evidence of metastasis[7].

The second type of multiple glioma classification is at the time the lesions occur. These are further sudivded into synchronous (when all the lesions are present at the initial time) and metachronous (when subsequent lesions occur months to years after the initial diagnosis of glioma) types[6].

Clinical manifestations

There is a wide range in age at presentation of multiple gliomas, but the majority of patients are of middle, or old age. No significant differences between sexes have been found. The clinical manifestations of multiple gliomas are variable and noncharacteristic, in relation to the extent of the lesions. Lafitte et al.[1] reported 8 cases with multiple glioblastomas, the major clinical manifestations included sensitivomotor loss (75%), aphasia (25%), seizures (12.5%), and headache (12.5%). In the series of Salvati et al.[7] studying 25 patients, there were neurological focal signs (72%), epilepsy (40%), and intracranial hypertension (68%).

Radiographic features

The radiographic features of multiple gliomas are non-specific. In general, iso-to hypodense lesions are seen on computerized tomography (CT) with a more or less diffuse mass effect, with no enhancement after intravenous contrast medium administration. However, CT may fail to show the condition, or to define its extent accurately. Due to its good tissue characterization properties and multiplanar imaging capacity, magnetic resonance imaging (MRI) provides better tissue contrast than CT, so it is more sensitive than CT for detecting lesions, and shows the extent of lesions better than CT. Generally, lesions produce a hypo- or isointense signal on T1-weighted images, and a hyperintense signal with T2-weighted images. Edema and mass effects are absent or moderate. After contrast media administration, the enhancement is mostly strong, often either heterogeneous, or ring-like. In some instances, meningeal or ventricular enhancement suggestive of a possible way by which dissemination can be observed[1,4].

The number of tumors in each patient can be range from 2 to 15. Kyritsis et al.[6] studied 51 patients with multiple gliomas: in 31cases (60.8%), there were 2 lesions; in 8 cases (15.7%), there were 4 lesions; in 9 cases (17.6%), there were four lesions; and in 3 patients (5.9%), there were more than 4. A study carried out by Salvati et al.[7] reported that 25 patients had mulcentric gliomas, 22 patients (88%) had 2 lesions, 1 patient (4%) had 3 lesions, and 2 patients (8%) had 4 lesions.

The topography of the tumor infiltration is not consistent. In the study by Kyritsis et al.,[6] a significant percentage of multiple tumors were found in the parietal lobe (37%), while the frontal and temporal lobes had 28% and 22%, respectively. Tumors were found less frequently in the occipital lobes, thalamus and brain stem. Even the spinal cord can be involved. Wahhabi et al.[8] reported a case with multicentric gliomas of the cervical cord. Either one or both of the cerebral hemispheres may be affected. No hemispheric predilection was identified. Tumors can also occur above and below the tentorium. In Salvati's[7] study, they were found in 9 (36%) of the 25 cases.

Pathology

Glioblastoma is the most frequent histotype of multiple gliomas. However, more benign glial neoplasms including astrocytoma and ependymoma have also been reported in multiple gliomas[9-14]. In the 51 cases reported by Kyritsis et al.,[6] there were 31 cases of glioblastoma multiforme, followed by anaplastic glioma (19 cases) and low-grade glioma (1 case). The lesions of multifocal gliomas are mostly the same histotype, whereas, multicentric gliomas may consist of several foci of the same histotype, or may be of different histotypes[7, 14, 15] In the series of Salvati et al.,[7] this occurrence was encountered in 6 (24%) of 25 cases. Michael et al.[16] reported a malignant multicentric tumor on histopathological examination in 2 of the 3 intracranial tumor sites revealing 2 different grades: the chiasmatic involvement showing an anaplastic astrocytoma (WHO III), and the right temporal tumor revealing a glioblastoma multiform (WHO IV). Few authors have reported a simultaneous growth of tumors of different cellular origins, such as prolactinoma, meningeoma, and glioblastoma[17], and as meningeoma, pituitary adenoma, and astrocytoma[18]. Furthermore, multiple gliomas can coexistence with tumors that originate from other organs, In a study by Salvati et al.,[7] there was a case in which multicentric gliomas were associated with one cerebellar metastasis from breast cancer. Based upon a small series of only 10 cases, Jomin et al.[19] stated that multicentric gliomas are of low grade malignancy, whereas high grade malignant gliomas usually result in multifocal involvement by early metastatic spreading. This finding is supported by a retrospective study showing a mean survival time of 10 months in 10 multicentric tumors and only 6 months in 30 multifocal tumors[4].

Pathogenesis

The pathogenesis of multiple gliomas remains unknown. Many pathogenetic theories have been suggested to explain multiplicity[6, 7, 9, 20, 21]. According to Cohnheim and Ostertag[9], the multiplicity depends on the activation of primitive cells with blastomatous potential, and are scattered throughout the nervous system during development. Zulch[22] stated that multiple

lesions are metastases from a primary focus via some pathway as yet unknown to us. The most recognized was that reported by Willis[23]. He contended that the evolution of multicentric gliomas is a two-step process. In the first stage, a large area, or perhaps even the entire brain undergoes neoplastic transformation (initiation), becoming more susceptible to neoplastic growth. In the second stage (promotion), a process of neoplastic proliferation in multiple sites occurs following various kinds of stimulation (biochemical, hormonal, mechanical, or viral). Despite the existence of many hypotheses, no single theory can fully explain the genesis of multiple gliomas.

Diagnosis and differential diagnosis

When patients have symptoms such as vertigo, nausea, or focal neurological deficits, and when neuroimaging reveals several lesions, a diagnosis of multiple gliomas should be considered. However, considering that the clinical manifestations and CT/MRI features are not definite, the diagnosis of multiple gliomas still remains problematical. The differential diagnosis from metastases, multiple lymphomas, necrosis, and vascular or demyelinating diseases is still very difficult. Metastatic disease and, until recently, multiple lymphomas represent the most important differential diagnosis. Some criteria can be used in distinguishing primary brain tumors from metastateses (Table 1)[1]. Multiple lymphomas usually demonstrate moderate spontaneous hyperdensity on CT. On CT and MRI they often are greatly enhanced by contrast media injection. Peritumoral edema is mostly weak, or absent. When several enhancing lesions with a mass effect are identified, an infectious cause should be considered (bacterial, fungal, or parasital abscess), especially in case of fever or immunodepression (toxoplasmosis). The abscesses are frequently surrounded by a peripheral ring which appears hypointense on T2-weighted sequences. Diffusion-weighted imaging can usually help in discriminating tumoral necrosis (hyposignal) from an abscess (hypersignal). The distinction between gliomatosis cerebri and multiple glioma is not clear, since foci of a true malignant glioma can occur in gliomatosis. Some features of radiology may help to discriminate between the two diseases. Multiple glioma tumor masses are found at different sites using strong contrast enhancement (often either heterogeneous or ring-like). Centro-tumoral necrosis, perifocal vasogenic edema, mass effect on ventricles and sulci, and centrifugal extension follow white matter tracts. However, these conditions seldom occur in gliomatosis cerebri[24,25].

A definite diagnosis of multiple gliomas should be confirmed by histopathological examination. Stereotactic biopsy represents a safe and satisfactory method for achieving sure diagnosis. It has become a powerful and safe tool for providing tissue samples for diagnosis with minimal disruption of normal brain function, and plays a significant role in the management of malignant brain tumors. Many other authors have pointed out that stereotactic biopsy is preferred over surgical biopsy in the diagnosis of the cranial lesions. In comparing common open biopsies with the stereotactic method, the following advantages are noted: only a small hole is made in the skull (no trepanation is necessary); deep targets can easily be accessed without significant brain damage; the precise location of the biopsy can be achieved; multiple biopsies can be taken at intervals along one or several tracks in order to determine the various aspects of the lesions in respect to size, limits, anaplastic foci, local variations, etc.[26,27]

Table 1. Comparative imaging features (CT and MR) for brain metatasis and multiple gliomas.

	Multiple glioma	Metastasis
Location	Mostly supratentorial spread by hemispheric pathways	Infra- and supratentorial cortex/ white matter junction
Size and shape	Often different	Often comparable
Peritumoral edema	Mild or weak	Important
Hemorrhage	Unusual	Frequent
Enhancement	Strong (++, heterogenerous)	Strong (++, ring shaped)
Margins (after injection)	Often indistinct	Variable

Table 2. Cases of multiple gliomas diagnosed by stereotactic biopsy.

Author	Publication time	No. of patients	No.of lesions	Histopathology
Franzini, A[28]	1994	12	-	-
Zaki, HS[29]	2004	2	-	glioblastoma multiforme
Mishra, HB[2]	1990	1	2	-
Pell, MF[3]	1991	1	2	anaplastic astrocytoma,1 glioblastoma multiforme, 1
Salvati, M[7]	2003	8	-	-

Thus far, only 6 papers have reported 24 cases with multiple gliomas diagnosed by stereotactic biopsy (Table 2). Franzini et al.[28] performed stereotactic biopsy on 100 cases with cranial multiple lesions. They found 12 cases of multiple gliomas, and Zaki et al.[29] reported 2 cases of glioblastoma diagnosised by stereotactic biopsy in 2004. In a study by Mishra et al.[2], two multicentric gliomas that had supratentorial and posterior fossa lesions were described, in which open and stereotactic biopsy was conducted in one case. Pell et al.[3] reported a case of a 11-year-old boy whose tumors were above and below the tentorium. He underwent stereotactic biopsy and the tumors were histologically confirmed. Of the 25 cases reported by Salvati et al.[7] 8 cases were histologically diagnosed using stereotactic biopsy. Although no statistical analyses comparing surgical biopsy with stereotactic biopsy in multiple gliomas have been reported, the advantages of stereotactic biopsy may also apply for the pathological diagnosis of multiple gliomas. It is our opinion that stereotactic biopsy for the purpose of obtaining pathological analysis for multiple gliomas will eventually replace open biopsy.

The distinction between multicentric and multifocal gliomas is difficult. With respect to multifocal gliomas, the appearance of multiple foci results most frequently from dissemination along the CSF pathway for the lesions in contact with subarachnoid or ventricular spaces. They can also result by spreading across the brain parenchyma, especially the corpus callosum. Thus, multiple locations that often occur concurrently are located in the same hemisphere, or close to dissemination pathways, and are histologically aggressive. However, autopsy remains the only method of establishing with absolute certainty whether the tumors have microscopic continuity. Barnard et al.[5] showed that whole-brain, celloidin-embedded sections used in conjunction with routine paraffin wax blocks are the only satisfactory method for establishing whether two tumours are microscopically distinct. Nissl's cresylic violet stain on the celloidin sections provides a reliable means of detecting microscopic foci and the extent of diffuse spreading. It may be helpful to ascertain if gliomas are multicentric, or multifocal, since in multicentric cases a more aggressive therapy can ensure longer survival time and a better quality of life.

Therapy and prognosis

The prognosis of multiple gliomas remains unfavourable. In the study by Salvati et al.[7], the average survival was 7.6 months (range 0.5~18) after diagnosis or, in the cases of metastasis, after the last glioma was detected. Current reports in the literature suggest that the diagnosis of multicentric rather than multifocal gliomas leads to a more aggressive therapy, ensuring longer survival. A retrospective studied by Salvati et al.[4] showed a mean survival time of 10 months in10 multicentric tumors and of only 6 months in 30 multifocal tumors.

The main problem with multiple gliomas is the treatment. Current opinion ranges from rejection of surgical treatment to its recommendation. Some authors advocate an aggressive approach with surgical removal for longer and better survival, considering adjuvant treatment to be more useful when the tumor bulk is already reduced[3,4,30], while some authors[13,26] think that biopsy must be the first protocol step, believing that extensive resection increases the risk of haemorrhage and neurological deficit without improving long-term survival. Currently, most researches have stated that a therapeutic plan should be made according to the nature of the lesions and patients. If lesions were large and had a marked mass effect, especially causing obvious intracranial hypertension, a craniotomy should be conducted as early as possible. Moreover, in the cases of multicentric gliomas, the lesions should be removed at one time, resecting as many as possible. Histopathologic examination of the lesions is always advisable if they are located in sites inaccessible to surgery[31].

If lesions are not large, causing no symptoms from a mass effect, or not occupying space in the eloquent cortex, stereotactic biopsy can be the initial step, after obtaining histological confirmation. Then chemotherapy and radiotherapy should be performed. Whole brain radiotherapy is preferable for multiple glioma patients. The chemotherapy schedule of multiple gliomas is similar to common single glioma. Baker et al. [32] reported on a case of a 44-year-old female with recurrent, multicentric, malignant gliomas who experienced a lengthy remission lasting more than 4 years. The patient initially sustained seizures caused by a biopsy-proven anaplastic astrocytoma of the frontal lobe. She was treated with radiation therapy and procarbazine-CCNU-vincristine (PCV). However, the tumor progressed and extended to the corpus callosum with a midline shift, refractory to four cycles of continuous 72-h infusion of BCNU/cisplatinum. Additional enhancing lesions appeared in the left frontal and left temporal lobes. Then she was started on sodium phenylbutyrate, 18 g daily in 3 divided oral doses, and reduced to 9 g/day and eventually to 4.5 g/day to eliminate a mild, reversible side effect. Four years later, the patient has a KPS functional score of 100%.

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