Are Metachronous Multicentric Gliomas Systemic or Metastatic Disease of the Brain? Case Report and Review of the Literature

Metakranoz Multisentrik Gliomalar Beynin Sistemik/Metastatik Hastalığı mıdır? Olgu Sunumu ve Literatür Taraması

ABSTRACT
A 40-year-old male had been operated five years ago due to a right frontal diffuse infiltrative astrocytoma grade II and the tumor had been removed grossly. There was no other lesion in the posterior fossa at that time and the patient received radiotherapy and chemotherapy. Five years later, the patient presented with an infiltrative intraaxial lesion in the left cerebellar hemisphere and vermis and superior to the right cerebellar hemisphere, also compressing the brainstem. After an emergency shunt procedure, the tumor was removed grossly. The histopathological examination revealed a grade III anaplastic astrocytoma. Whether multicentric gliomas (MCG) develop following metastasis with an unknown pathway, or whether they are multifocal and should be considered as a systemic disease of the brain, is open to discussion. We suggest that this pathological condition should be accepted as a systemic disease of the brain. Radiotherapy may induce new tumor foci. The treatment should always be aggressive removal.

KEY WORDS: Glioma, multicentric glioma, multiple cerebral lesions, multiple glioma

ÖZ

ANAHTAR SÖZCÜKLER: Glioma, multisentrik glioma, multipl serebral lezyonlar, multipl glioma
INTRODUCTION

Multicentric gliomas (MCG) exist in different regions of the brain independent from each other and are different entities than multiple gliomas. The incidence is 2.3-9.1% (1, 2, 4, 6, 7, 8, 10, 11, 12, 13). They may be located in different lobes and hemispheres. Their supra- and infratentorial existence is extremely rare (15, 16, 22). MCG which are demonstrated at the same time are called ‘synchronous’ and if there are days or years between the lesions they are called ‘metachronous’ (19, 22). The development theories are still open to discussion and different treatment protocols are used by different neurosurgery clinics. Here, we present a metachronous supra-infratentorial MCG. The main discussion point of this case is whether the tumor spreads via an unknown pathway or whether there multiple foci. Should this pathological entity be accepted as a systemic or metastatic disease of the brain?

CASE REPORT

A 40-year-old male presented to our clinic with headache five years ago and his radiological evaluation revealed a mass lesion in the right frontal lobe (Figure 1). His neurological examination was normal. He was operated on via a right frontal craniotomy and the tumor was removed grossly. The histopathological examination at that time revealed diffuse infiltrative astrocytoma grade II. The patient received radiotherapy and chemotherapy with procarbazine, CCNU and vincristine. The postoperative magnetic resonance imaging (MRI) of the patient demonstrated gross total removal of the tumor. There was no other lesion in the posterior fossa at that time (Figure 2).

Five years later, the patient presented again with headache. His neurological examination revealed only cerebellar ataxia. On the same day, the patient’s neurological status deteriorated rapidly and he became confused and unconscious. The computed tomographic (CT) scan revealed acute hydrocephalus due to a mass lesion in the posterior fossa which was obstructing the fourth ventricle. The MRI scan of the patient shortly after the surgical procedure demonstrated an infiltrative intraaxial lesion in the left cerebellar hemisphere and vermis and superior to the right cerebellar hemisphere, also compressing the brainstem. There was also a cystic lesion in right frontal lobe which corresponded to the location of the previously operated lesion (Figure 3). An emergency cysto-ventriculo-peritoneal shunt procedure was performed. The patient’s neurological status improved 3 days after the shunt procedure. The histopathological study of the cerebrospinal fluid (CSF) obtained by lumbar puncture revealed no tumor cells. He was operated on via a lateral suboccipital approach and the tumor was totally removed grossly. The patient recovered well after the operation. A surgical procedure was not planned for the right frontal cystic lesion. The histopathological examination revealed grade III anaplastic astrocytoma. The patient is now being followed-up by the oncology department.

Figure 1: Preoperative T1 and T2 axial, and T2 coronal MRI scans of a 40-year-old male demonstrated a right frontal cystic lesion surrounded by mild brain edema. There was no other lesion in the posterior fossa at that time.
although the incidence in different publications is between 3% and 9%, many cited cases of multicentric gliomas in previous series should actually be classified as multifocal (2, 3). On the other hand, some of them may have been misdiagnosed as a metastatic tumor and their incidence might have been underestimated (1). Differential diagnosis with brain abscesses, lymphoma, infections, and demyelinating and vascular diseases may also be difficult. MRI scan helps in the differential diagnosis and shows tumors not demonstrated on CT scan (8). Histopathological examination of all brain sections by autopsy studies provides accurate results on the location and foci of MCG. Scherer is the only author who examined all brain sections (17) and there is a lack of autopsy studies in the literature. MCG are more commonly located in the same hemisphere but they may also rarely be seen supra- and infratentorially. The etiology and theories are still open to discussion (11, 12, 13, 15, 16, 22). Zülch proposed that multicentricity may depend on some unknown metastasis pathways (23). Cohnheim suggested that the reason may be the activation of primitive cells which have blastomatous potential during development of the central nervous system (7). Willis pointed out that both mechanisms may play a role in the occurrence of MCG. He stated that the initial mechanism was the existence of a wide area under effect of neoplastic transformation. Then, tumor proliferation in two or more zones due to different stimulations (chemical, hormonal, viral) occurred (21). It was also pointed out that diseases such as multiple sclerosis and von Recklinghausen’s disease may predispose to the occurrence of MCG (15). Batzdorf and Malamud offered

**Figure 2:** Postoperative T1 axial MRI scans showed gross total removal of the tumor, with no additional lesion in the posterior fossa.

**Figure 3:** Five years later, axial, coronal and sagittal MRI scans of the same patient revealed a mass lesion in the left cerebellar hemisphere extending to the peduncle. A cystic lesion which corresponded to the location of the previously operated lesion was also demonstrated.

**DISCUSSION**

Budka classified multiple glial tumors into four categories in 1980: diffuse, multiple, multicentric and multiple-organ (5). Actually, it was Virchow in 1864 (20) and Bradley in 1880 who first mentioned multicentric gliomas (4). Their incidence was reported first by Russel and Rubinstein as 4.5% macroscopically and as 6% microscopically (14). Although the incidence in different publications is between 3% and 9%, many cited cases of multicentric gliomas in previous series should actually be classified as multifocal (2, 3). On the other hand, some of them may have been misdiagnosed as a metastatic tumor and their incidence might have been underestimated (1). Differential diagnosis with brain abscesses, lymphoma, infections, and demyelinating and vascular diseases may also be difficult. MRI scan helps in the differential diagnosis and shows tumors not demonstrated on CT scan (8). Histopathological examination of all brain sections by autopsy studies provides accurate results on the location and foci of MCG. Scherer is the only author who examined all brain sections (17) and there is a lack of autopsy studies in the literature. MCG are more commonly located in the same hemisphere but they may also rarely be seen supra- and infratentorially. The etiology and theories are still open to discussion (11, 12, 13, 15, 16, 22). Zülch proposed that multicentricity may depend on some unknown metastasis pathways (23). Cohnheim suggested that the reason may be the activation of primitive cells which have blastomatous potential during development of the central nervous system (7). Willis pointed out that both mechanisms may play a role in the occurrence of MCG. He stated that the initial mechanism was the existence of a wide area under effect of neoplastic transformation. Then, tumor proliferation in two or more zones due to different stimulations (chemical, hormonal, viral) occurred (21). It was also pointed out that diseases such as multiple sclerosis and von Recklinghausen’s disease may predispose to the occurrence of MCG (15). Batzdorf and Malamud offered
some criteria to differentiate MCG from multiple gliomas. These criteria were: a) no gross and microscopical connection between the lesions, b) tumor foci are not satellites of the primary lesion, and c) tumors spreading via the cerebrospinal fluid (CSF), the median commissural pathways (corpus callosum, fornix, septum pellicudum), internal capsule and massa intermedia should be excluded (2). The most frequently seen histopathological pattern is glioblastoma multiforme (15, 16, 22). MCG usually show the same histopathologic pattern but different types and grades have also been reported, as in our case, (2, 10, 11).

Recurrence of the tumor may be through the CSF pathway, radiation induction, radiation necrosis or new tumor foci. As stated before, tumors spreading through the CSF pathway should be excluded according to the Batzdorf-Malamud criteria. In our case, there was no dissemination through the CSF pathway. No tumor cell was encountered during histopathological studies of the CSF.

Radiation plays an important role for new tumor occurrence. Interestingly, in Salvati’s series of 25 cases with MCG, four had metachronous lesions all of whom had received postoperative radiotherapy after the first operation (15). Djallilian et al. also stated that 6% of the cases in their series had metachronous lesions, all of whom had received postoperative radiation treatment (8). Our case had also received radiotherapy after the first operation. Do these lesions represent radiation-induced tumors (9) or are there new tumor foci? Does the injury to previously treated normal brain (radiation, infection, etc.) increase the risk of new tumor occurrence? Do glial tumor cells travel first to a new site and then grow as a new tumor (18)? We suggest that multiple tumor foci may be present in cases with genetic predisposition to tumor occurrence. Therefore, genetical studies should be performed routinely on every MCG case. Some authors recommend aggressive removal of these lesions (15) while some suggest that biopsy, stereotactic or open, should be the first choice for treatment (6, 10). Extensive tumor removal may increase the risk of a postoperative neurological deficit. On the other hand, aggressive removal provides longer survival (15, 22). External beam radiation therapy for the treatment of the secondary lesion is risky because it may cause injury to previously treated normal brain (8). Stereotactic radiosurgery to the tumor margin without exposing adjacent brain tissue may be more feasible for the treatment of these lesions. We tried to remove as much tumor tissue as possible during the first and second operations. Although tumors in eloquent areas may be treated with stereotactic radiosurgery, aggressive removal is essential for longer survival.

In conclusion, we suggest that MCG should be accepted as systemic disease of the brain. There may be multiple tumor foci and the disease may occur independently from the initial location. Recent injury to the brain or radiotherapy may induce recurrence of the tumor.

REFERENCES


