

## Multicentric Glioma: Problems & Interpretations

YOUSSEF FARES, MD, Ph D\*†; MAHMOUD YOUNES, MD§; ALI KANJ, MD†;  
P. RUIZ BARNES, MD\*; JESÚS MUÑIZ, MD, Ph D\*

The authors report four patients suffering from multicentric intraparenchymatous malignant glioma lesions located in different regions of the brain. The incidence of multiple, separated, independent, non-connected neuroepithelial tumors in the same patient is rare, although a discrepancy exists in the literature with regard to its real incidence. There is also controversy with respect to the histological composition of these tumors. In some cases, identical

histopathological composition has been found, while in others different cellular patterns are present. Several hypotheses have been put forward to try to explain the occurrence of multicentric glioma tumor in the same patient. They consist of disseminations (through white matter tracts, cerebrospinal fluid pathways, or metastatic satellites around the vicinity of the tumor) or simultaneous development of different tumors, independent from each other.

In 1936, Courville (1) reported that around 9% of all gliomas are multiple, while other authors (2-6) believe that such estimation is excessively high, and the real incidence shall never be more than 2.5%.

The multiple, simultaneous, or successive appearance of glial tumors having identical histology or different neuroepithelial histopathology in the same patient is a very rare experience (7). Manzini, et al. (3) found multiple gliomas in 5.3% of all intracranial neoplasms. Multicentric gliomas have been encountered in 0.05-0.06% of autopsies. According to Schiefer, et al. (8) the incidence of multiple gliomas is 0.5 and 1 per one thousand.

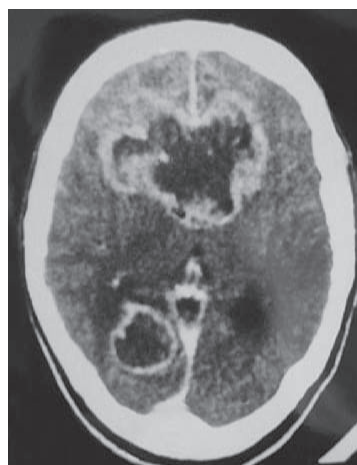
Budka, et al. (9) described an occurrence of multiple gliomas of 3.1% in 96 patients gravely ill with primary neuroepithelial brain tumors. Bastian, et al. (10) found one case with a multicentric glioma in his series of 15,000 autopsies. Tanghetti, et al. (11) observed 3 cases of multiple focuses within a series of 120 patients with glial tumors. Pezeskpour, et al. (12) reported primary intracranial tumors with secondary subarachnoid colonization in 0.01% of the cases at initiation of signs or diagnosis.

Therefore, discrepancy exists in the literature with regard to its real incidence and occurrence of multicentric gliomas. On the other hand (12, 14-26) we are not aware of any scientific reports that have studied the etiology and causes promoting the development of multicentric gliomas.

### Materials and methods

#### Case N° 1:

This is a seventy-year old female, with an unremarkable personal history, who 6 weeks before hospital admission in August 1989, developed an acute episode of confusion, incontinence, and deterioration of the superior cortical functions. A medical evaluation revealed hyperglycemia. During the hospital stay, she developed left hemiparesis, followed by focal seizure. She underwent a cranial CT scan showing a large size brain tumor lesion in both frontal lobes, connected by the corpus callosum with an outlining ring of enhancement in addition to central hypodensity. Another lesion having the same characteristics was present in the right parieto-occipital area with mass effect (Figure 1). A biopsy of the lesions was compatible with glioblastoma multiforme, (astrocytoma, grade IV). An immunohistochemistry revealed necrotic tissues.



**Figure 1.** Multicentric astrocytoma, lesion of great size in both frontal lobes, crossing the callosal body with an outlying ring capturing contrast. Another lesion of the same characteristic appears at the right parieto-occipital area.

\*Department of Neurosurgery, Clínica Ntra. Sra. de la Concepción (Fundación Jiménez Díaz), Universidad Autónoma Madrid, España. †Department of Neurosurgery, Hammoud Hospital, University Medical Center, Sidon, Lebanon. §Department of Neurology, Al Rassoul Al Aazam Hospital, Beirut, Lebanon

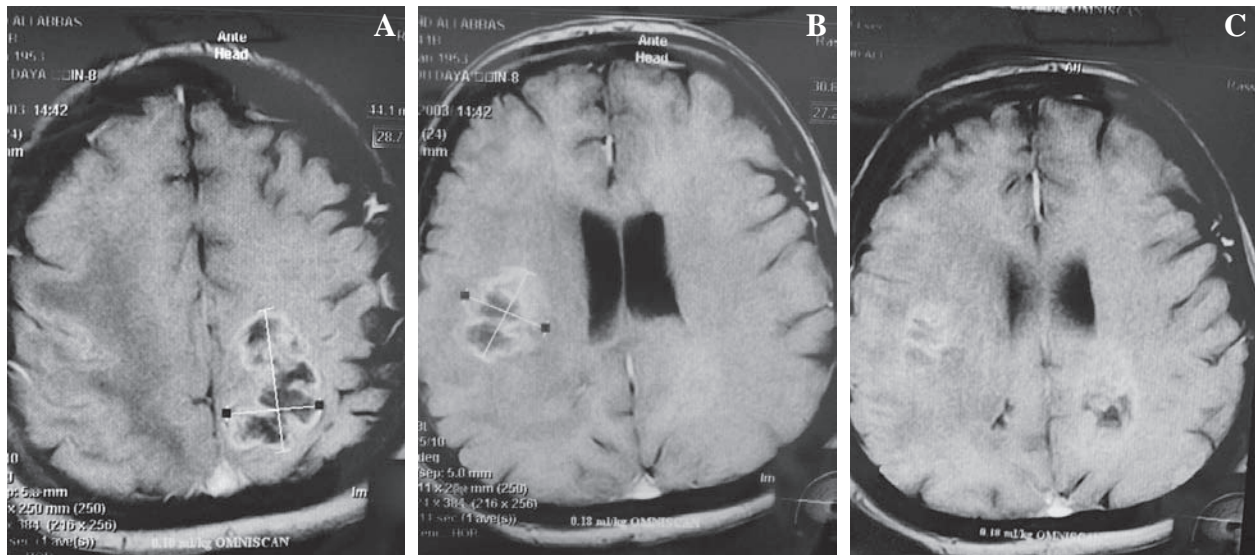
Address correspondence to: Youssef Fares MD, Ph D, Neurosurgical Department, Hammoud Hospital, University Medical Center, Sidon - Lebanon. Fax: 00961-7-725833 • Email: fpmnet@yahoo.com

Initially, the patient improved with steroid treatment, but her diabetes mellitus control became aggravated. She developed focal seizures too difficult to control, followed by deterioration of her level of conscience, until she died.

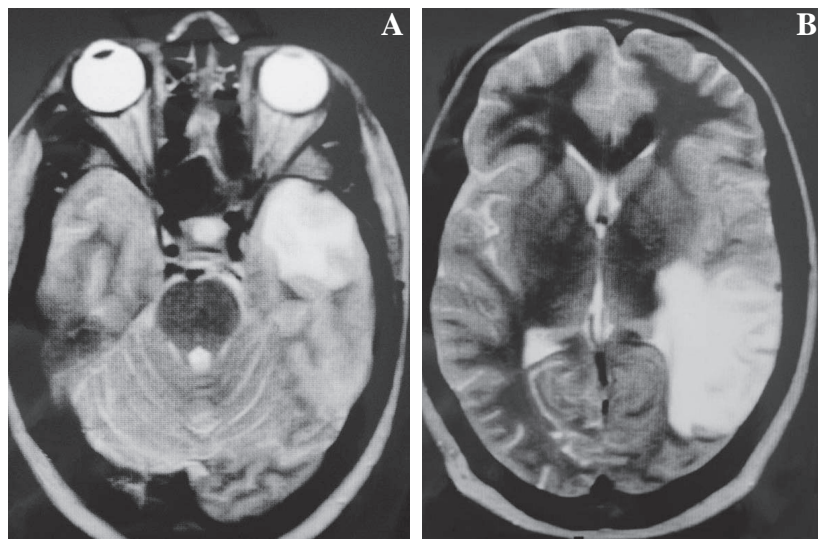
**Case N° 2:**

This is a 51 year-old female patient who in September 2002 developed an episode of acute confusion associated with lack of concentration. She also suffered 3 episodes of epileptic seizures. The MR imaging showed a left

parietal lesion, and a second lesion was located in the right parieto- temporal region (Figures 2A, B and C). On September 2002, she underwent a craniotomy with partial excision of the left parietal lesion. The pathology was compatible with “astrocytoma grade II”. The right percutaneous biopsy gave the same result. A cerebral MR imaging, 3 months after surgery, showed stable lesions. Nine months after the surgery, the radiological studies demonstrated progression of the tumoral lesions. The patient died 20 months after the first operation.



**Figure 2.** Astrocytoma grade II. with two lesions, one a left parietal lesion at the level of the right hemisphere (B). The two lesions are seen under a single court (C)



**Figure 3.** Astrocytomas of low degree in the left hemisphere, without continuous connection.

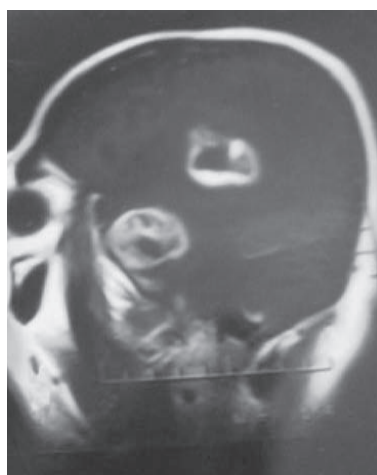
**Case N° 3:**

This is a 29 year-old female patient with an unremarkable medical history that, on April 2004, presented to the outpatient clinic complaining of repeated migraine headaches. Her headaches did not improve with conservative treatment. Subsequently, she presented an episode of severe headache crisis. A CT scan imaging showed a basal left temporal hypodense lesion and a second lesion over the temporo-parietal region on the same side (Figures 3A and B). Biopsies were simultaneously made of both lesions in May 2004. The pathology report documented compatibility with low grade astrocytomas. The patient subsequently underwent radiotherapy.

Currently, the patient has remained stable without neurological deficits, under medical supervision.

#### Case N° 4:

This is a 67 year-old male patient that was evaluated at the outpatient clinic during July 2004 with fluctuating confusional status. An MR Imaging detected a right temporal tip lesion and another lesion at the level of the Sylvian Fissure on the same side (Figures 4). Three weeks later, the patient's neurological condition deteriorated quickly, but his family declined any surgical intervention or biopsy. The patient continued to deteriorate until he eventually passed away.



**Figure 4.** Possible multiform “astrocytomas” in the same hemisphere, of similar high degree (Fig. 3) in a 29 years old female with low degree “astrocytomas”.

## Discussion

The terms “multiple, multilocular and multicentric gliomas” are not applied in a homogeneous way in the literature. The multiple, simultaneous, or successive appearance of tumors with identical histology or different neuroepithelial histopathology in the same patient, is a very rare occurrence. Several case reports and small clinical cohorts have been published in the medical literature and discrepancy exists regarding its real incidence and development.

First Carville (1), and later-on Hildebrandt, et al. (7) and Matador and Malamute (2) were among the first to talk seriously about the possibilities of multiple intracranial lesions. Bollinger (27) and Fried (28) presupposed, with regard to applying the term “multicentric”, a relationship must exist at least histologically demonstrating between the different tumors cells.

Bastian, et al. (10), Busson, et al. (29), Heuch, et al. (30), Jomin, et al. (31), Loseke, et al. (32), Rao, et al. (33), Salles, et al. (34) and Tanghetti, et al. (11) have agreed on the term “multicentric glioma”, emphasizing the multicentric

growth of these lesions, and, therefore, the existence of an anatomical relationship between the tumor areas.

Busson, Heuch, Jomin, and Loseke were in agreement with the definition of multicentric tumors. They were concerned that this phenomenon could be related to a dissemination of the tumors through “commissural” unions, such as the callosal body, or through the formation of satellites close to the main tumor.

Borovich, et al. (35) understood as “multifocal” the simultaneous growth of different tumors without any anatomical relationships.

Solcher, et al. (36) spoke about multiple intracranial tumors, when multiple gliomas appear in different places.

Hildebrandt, et al. (7) have summarized the multicentric gliomas with respect to genesis and diagnosis:

- 1) Primary lepto-meningeal gliomatosis is the origin of “glial” hetero-topical and in the secondary lepto-meningeal gliomatosis (36-37), a question of multiple lesions being gliomas from the same primary lesion.
- 2) The combination of multiple gliomas with progressive “leucoencephalopathy” (24, 38) or multiple sclerosis (12, 33, 39, 40) points out a genesis starting from an inflammatory or immunological process (41). We have not observed any such type case.
- 3) Diffuse gliomatosis of the brain (42) or “gliomatosis cerebri” (43).
- 4) Glioblastomas consecutive to radiotherapy of neuroectodermal tumors (44).
- 5) Successive multiple glial tumors with identical histology (45).
- 6) The combination of supra and infra tentorial localization. According to Loseke, et al. (32) there are only 17 cases in the literature.
- 7) Gliomas of the brain and the spinal cord of different or identical histology occur less frequently, as the case reported by Reichenthal, et al. (46).
- 8) “Meningeal” sarcomatosis with multiple glioma can occur in four different ways as reported by Moya, et al. (47):
  - The sarcoma starts from the glioma, in the region of the infiltrating glioma.
  - These were “sarcomatosal” modifications in the region of the fibrous leptomeningeal reaction, in the area of the infiltrating glioma.
  - Glioma occurrence as a neoplastic modification in the area of the reacting astrocytic near a sarcoma.
  - Tumors have an independent genesis.
- 9) Collision tumors described by Molnar, et al. (48) and Solcher, et al. (36): According to the latter, “glial” tumors can produce secondary neoplastic modifications in the neighboring tissue.

- 10) Phacomatosis, Rodríguez, et al. (49) found glioma in 45% of cases of neurofibromatosis.
- 11) The term multifocal glioma was described by Rao, et al. (33) after some exceptional case of an increase in the focuses of glioma after an operative intervention.

A classification of different types of multiple lesions of the nervous system made by Budka, et al. (9) is shown in Table 1.

**Table 1.** Classification of different types of multiple lesions made by Budka, et al.

1. Multiple gliomas without continuous connection.	2. Multiple gliomas with continuous connection demonstrable histopathologically.
1.1. Glioma with metastasis, through CSF path.	2.1. Multicentric glioblastomatosis (diffuse involvement of most of the brain with multiple nodular condensations in the center).
1.2. Primary multiple glioma (without continuous connection or spaces irruption of CSF, especially if different histology exists).	

Case 1 shows a high grade astrocytoma and cases 2 and 3 reveal a low grade astrocytoma. This tumor can become more aggressive as shown in case 2 in which, 9 months after surgery, multiple lesions were noticed, although no biopsy or autopsy were performed. The above cases fit into the classification 1.2 shown in Table 1, as reported by Budka, et al. (9).

We can distinguish multicentric tumors from multiform tumors. We define multicentric tumors as a neoplasm with simultaneous growth of independent tumors and no anatomical relationships. Multiform tumors are glial tumors that disseminate through white matter tracts (via commissural, callosal body, internal capsule, massa intermedia), or cerebrospinal fluid (including the subarachnoid spaces and ventricular system), or from metastatic tumor satellite lesions or brain edema.

From our speculation, it is reasonable to assume, that in tumors at different lobes or hemisphere without gross evidence of dissemination, there is a possibility that these may form and develop independently from one another. These tumors can be classified as multicentric tumors (Table 2).

However, unless a histological analysis of both tumors is done, it will be highly speculative to decide between multicentric or multiform tumors.

We observed that cases 1 and 2 can fit into multicentric astrocytoma, but there is no definite histological proof. While cases 3 and 4 could be considered an astrocytoma multiform.

The modern treatment of glial tumors is multi-specialty, involving surgery, radio and chemotherapy. While surgery regarding multicentric tumors is not ideal, it is important that tissue diagnosis is established, and perhaps in the future, establish the genetic profile of each tumor as well. Although many other therapeutic measures are based on histopathological diagnosis, in certain instances it can be based on the neuroradiological study.

**Table 2.** Classification of different types of multiple lesions made by Fares, et al.

Tumor	Description
<b>Multicentric Tumors</b>	Simultaneous growth of independent tumors without anatomical relationships.
<b>Multiform Tumors</b>	Dissemination via commissural, callosal body, internal capsule, massa intermedia or via CSF or for subarachnoid spaces or ventricular system or for metastatic satellites or through brain edema.

In our opinion, we have to keep in mind that our knowledge on the mechanism of the origin, growth, and extension of cerebral tumors is yet limited, but hopefully we will gain more knowledge and eventually learn how to cure this tumor.

## Resumen

La aparición múltiple (simultánea o sucesiva) de tumores idénticos desde el punto de vista histológico o de génesis neuroepitelial distinta en el mismo paciente es un hallazgo raro. Existe discrepancia en la literatura en cuanto a su incidencia real (fluctúa entre 2-9%). El hallazgo simultáneo de varias lesiones del sistema nervioso central en un mismo paciente puede ser debido a diseminación (vía comisural, líquido cefalorraquídeo o metástasis). Sin embargo, en otros casos, dicho hallazgo no se puede explicar por diseminación, al situarse separados en lóbulos o hemisferios diferentes. En dichos pacientes, se pueden originar sendos tumores independientes uno de otro. Se presentan 4 pacientes en los que coincidían varias lesiones independientes en diferentes partes del sistema nervioso central.

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