Multicentric glioblastoma multiforme. Report of 3 cases, clinical and pathological study and literature review

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Abstract
Multicentric gliomas are uncommon lesions of the central nervous system. Their management remains controversial, but histopathologic diagnosis after complete or partial resection must be performed to differentiate these tumors from other multiple cerebral lesions. Three cases of multicentric glioma are presented, one of which had suprat- and infratentorial lesions. Histological specimens were obtained from removal of at least one of the lesions. Neuropathological examinations confirmed the diagnosis of grade IV malignant glioma (glioblastoma). All 3 patients died soon after symptom onset. However, one patient, with metachronous glioblastomas, had a comparatively long survival. We discuss the patho-genetic hypotheses and the diagnostic problems, especially the differential diagnosis from other multifocal diseases of the central nervous system.

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Glioblastoma multicéntrico. Descripción de 3 casos, estudio clinicopatológico y revisión de la literatura

Resumen
Los gliomas multicéntricos son lesiones inusuales del sistema nervioso central. Su manejo sigue siendo controvertido y es necesario un diagnóstico histopatológico tras su resección parcial o completa para diferenciarlos de otras lesiones cerebrales múltiples. Se presentan 3 casos de glioma multicéntrico, uno de ellos con lesiones supra e infratentoriales. Se obtuvieron muestras histológicas tras resección de al menos una de las lesiones. Análisis histopatológicos confirmaron el diagnóstico de glioma maligno grado IV (glioblastoma). Los 3 pacientes fallecieron en breve periodo de tiempo tras la aparición de los síntomas. Sin embargo, uno de ellos, con glioblastomas metacronos tuvo, comparativamente, una...
Introduction

Multicentric gliomas are well-separated lesions, located in different lobes or hemispheres, which cannot be ascribed to dissemination through commissural pathways, cerebrospinal-fluid (CSF), blood or local extension.\(^1\)\(^2\) They must not show continuity with different lesions (microscopically or macroscopically), and should not be satellite lesions of a primary tumor.\(^3\)\(^4\) When these conditions are not met gliomas are called multifocal.\(^3\)\(^5\)

Case report

Case 1

A 79-year-old woman was admitted because of severe headache and fluctuating motor dysphasia. She had no clinical history of note. Computed tomography (CT) scans and magnetic resonance (MR) images showed at least 5 independent mass lesions in the left frontal, temporal and parietal lobes. Another lesion was situated in the right pons (Fig. 1). A diagnosis of cerebral metastases was ruled out after thoraco-abdominal CT, whole-body positron emission tomography (PET) and digestive endoscopic studies. Surgical removal of the frontal lesion determined that this was a glioblastoma. We therefore concluded that she had a multicentric glioblastoma.

The postoperative period was unremarkable. No adjuvant radiotherapy was given because of the age and clinical situation of the patient and the evidence of multiple lesions. Three months after symptom onset the patient experienced worsening of her neurological and general situation and finally died.

Case 2

Neurological examination of a 39-year-old man revealed obnubilation, global aphasia and left hemiparesis. A cranial CT showed a right parieto-temporo-occipital lesion of \(4 \times 3\) cm, with peripheral contrast enhancement, and surrounding cerebral oedema with midline shifting. A MR study showed the same lesion and also revealed multiple small left parieto-temporal lesions. (Fig. 2) We performed a subtotal surgical resection of the right parietal lesion.

During the immediate postoperative period the patient continued to have a low conscious level. Electroencephalography (EEG) determined left hemisphere paroxysmal activity. A CT showed a right temporo-occipital infarction that was treated medically. (Fig. 3) Histological examination revealed the presence of a grade IV glioma. After hospital discharge whole brain radiation was performed. The patient died 5 months after the first hospitalization.

Case 3

A 54-year-old man presented with a two-month history of headache and dizziness. The neurological examination revealed right homonymous quadrantapnia. CT scans and MR images showed a left parieto-occipital lesion with annular contrast enhancement, and peripheral oedema. (Fig. 4) After surgical removal of the main lesion, histological examination confirmed the diagnosis of glioblastoma.

One month after surgery, when the patient was attending for the radiotherapy consultation, a routine T1 weighted control MR revealed a left frontal hypodense lesion with heterogeneous contrast enhancement, similar to the original images of the resected lesion. Comparison with the earlier CT images suggested that this frontal lesion was a new tumor,

Fig. 1 – (Left) T1 weighted MR with contrast enhancement showing one parasagittal frontal lesion, and a second lesion on the parahippocampal gyrus. (Right) The same lesion on the left parahippocampal gyrus and another lesion on the pons.
separate from the occipital lobe tumor. The patient underwent left frontal craniotomy with total resection of the lesion. Pathological analysis revealed a multicentric glioblastoma. Adjuvant therapy was given with whole-brain radiotherapy and chemotherapy with temozolamide. Nine months after the onset of the clinical disturbance the patient died.

Discussion

Multiple gliomas are considered to be gliomas spreading through commissural or other pathways such as the fornix and the corpus callosum, through cerebrospinal channels, and/or by local metastasis.6

Multicentric brain tumors of glial origin are encountered infrequently, with reports suggesting they account for 0.15–8% of glial tumors.1,5,7 Most of these tumors are located in the supratentorial compartment, though multicentric glial tumors have also been found supra- and infratentorially, which is unusual, and is thought to define a multicentric glioma as well.6,8-10

Nothing is known about the pathogenesis of these multicentric gliomas. Among the several aetiopathogenic theories is that of Conheim, who suggested multiple embryonic residues scattered at different sites.8 Based on this theory, Ostertag considered that gliomas grow from primitive cells displaced during the development of the central nervous system.1,11 Willis suggested two phases; the first of neoplastic transformation of a large area of brain tissue, and the second, a process of progressive neoplastic proliferation at different sites.12,13

Based upon a small series of only ten cases,14 the hypothesis was stated that multicentric gliomas are of low-grade malignancy whereas high-grade malignant gliomas usually result in multifocal involvement by early metastatic spread. Nevertheless, distinction between multicentric and multifocal gliomas is difficult. Zülich suggested that multicentricity is due to metastasis along some unknown pathway.15 Zülich15 identified 4 different patterns: Type I: Leptomeningeal dissemination: Leptomeningeal enhancement with or without CSF positive cytology for neoplastic cells. This pattern can itself be divided into 2 different groups: nodular (Type Ia, presence of mass lesion along the CSF cisterns) and diffuse (Type Ib, diffuse leptomeningeal enhancement). Type II: Subependymal dissemination: Ependymal enhancement with or without the presence of CSF cytology for neoplastic cells. Type III: Satellite tumor: The presence of nodular tumor distant from the primary lesion. This dissemination pattern also has 2 subgroups: Type IIIa, the presence of connection to the classic commissural pathways of dissemination; and Type IIIb, the absence of connection to the classic commissural
pathways of dissemination. And finally, Type IV: Mixed: A combination of the previous types.

Based on just histological findings, multiple gliomas have not been shown to have special characteristics that can differentiate them from a single lesion.\(^3\) The most frequent histological subtype found in multiple gliomas is glioblastoma.\(^3,16,17\) Glioblastomas are usually sporadic and develop de novo in the majority of patients ("primary" glioblastoma), or progress from a previously diagnosed low-grade or anaplastic glioma ("secondary" glioblastoma).\(^18\) Multicentric glioblastomas frequently contain lesions with different histopathological grades: glioblastoma (WHO IV), anaplastic astrocytoma (WHO III), as well as lower grades.\(^7,19\) Multicentric tumors can be defined as either synchronous or metachronous in their clinical presentation, the difference being that metachronous lesions do not overlap in time.\(^12\)

The age at presentation of a glioblastoma ranges from the 30s to the 70s, with no difference between single and multiple gliomas.\(^3,5,19\) Multifocal or multicentric high-grade cerebral gliomas seem to be slightly more common in men than in women (3/2) though some authors found no differences.\(^5,21\)

Multiple sclerosis or Von Recklinghausen's disease are considered entities that predispose to the development of multiple gliomas.\(^12,17\) The most frequent location of multiple gliomas is the frontal and parietal lobe, followed by the temporal lobe.\(^3,20,22\) Most patients present 2 or 3 lesions, though as many as 15 lesions have been described.\(^23\)

Multicentric glial tumors should be distinguished from multifocal tumors. When intracranial multiple lesions are found, metastatic brain tumors must first be considered.\(^10,11,20,24\) With the advent of AIDS, infectious and inflammatory lesions have become important, as well as neoplastic lesions like primary lymphoma f the central nervous system.\(^3\)

Tassel et al.\(^22\) described the radiological features, characterizing the lesion as having a deep location or outside the cortical–subcortical boundaries, as a solid nodule without central necrosis, and with an irregular shape but not suggestive of metastasis, favoring the diagnoses of multicentric glioblastoma. Ozawa et al.\(^24\) studied MR images and confirmed that multiple gliomas usually appear outside the cortical–subcortical boundaries, deep within the white matter of the brain. These authors also noted that contrast enhancement was more dense and oedema more extensive than in metastasis.

Detection of early lesions by a neuroradiological method, such as CT and MRI, may not prove the definitive existence of a brain tumor or discriminate neoplastic tissues from oedema.\(^2\) CT or MRI cannot reliably identify isolated tumor cells outside contrast-enhanced areas in the brain.\(^21,25\) PET scanning allows for the discovery of very small lesions by measuring the glucose utilization of a tumor that might go undetected with normal scans.\(^26,27\) Jawahar et al.\(^2\) reported that earlier PET can aid diagnostic decisions and subsequent treatment management in conjunction with MR examination.

The management of glioblastoma remains controversial. The tumor should be surgically removed whenever possible and some authors recommend early aggressive surgical removal of easily accessible tumors with a mass effect. Histopathologic examination of the lesions is always advisable if they are located at sites inaccessible to surgery. Stereotactic biopsy represents a safe and satisfactory method for achieving sure diagnosis.\(^23\)

Kotwica and Papierz\(^7\) suspected that a high number of multicentric or multiple gliomas had been diagnosed previously as metastatic brain tumors on CT scanning without histological verification. It is therefore important to investigate the histology of these tumors to achieve a correct prognosis and because in cases of glioblastoma we need high doses of radiotherapy, even more than in patients with metastases.\(^20\)

No report has yet linked either whole brain radiation (WBRT) or limited field irradiation to an improved overall survival rate or elucidated post-treatment failure patterns in these particular individuals,\(^21\) though limited doses are preferred as they can be delivered safer to whole brain fields.\(^23,28,29\) In the absence of a clear advantage to WBRT, clinicians might elect to use this approach for patients with a poor performance status who are unable to complete a prolonged course of radiotherapy.\(^29\) For other patients with multifocal glioblastoma and a good performance status, it might be preferable to avoid WBRT in favor of three-dimensional conformal radiotherapy (3D-CRT). Similarly, Djalilian et al.\(^30\) recommended radiosurgery techniques in metachronous glioblastomas to minimize the deleterious
effects of radiation on a field that has been recently irradiated. However, there is no variation in either first or second line chemotherapy regimens. Results from a review of the literature and our cases show that most patients die approximately 6–8 months after the onset of symptoms, though in some studies the outcome was worse, ranging from 2.8 to 4.8 months. Nevertheless, some patients with low grade tumors had a comparatively long life span after the onset. In addition, metachronous glioblastomas have been associated with a better prognosis, with histopathological studies finding clear differences between different tumors in the same patient.

**Conclusion**

Multicentric gliomas must be considered in the differential diagnosis of multiple lesions. Stereotactic biopsy is probably the best option to allow histopathologic examination in cases where lesion removal is not advisable. The treatment is palliative, and management is controversial. The prognosis, however, remains unfavorable.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

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