Multifocal high-grade gliomas constitute an uncommon clinical entity that poses diagnostic and treatment dilemmas. Here we describe the approach to these central nervous system tumors and the management of a series of four clinical cases. We emphasize the necessity for biopsy soon after symptom onset, to differentiate multifocal gliomas from brain metastases and thus plan individualized treatment. As imaging accuracy increases, so does the reported incidence of diagnosed multifocal lesions. We review the current pathogenetic hypotheses and the clinical characteristics and problems arising from these tumors.

**PRESENTATION OF CASES**

**Case 1**

A 64-year-old female presented with progressively worsening left hemiparesis and dysarthria. She had a history of osteoporosis, hyperlipidemia and mild bilateral internal carotid stenosis. Brain computed tomography (CT) scan revealed two hypodense lesions, one contrast-enhancing with surrounding significant edema close to the right primary motor cortex, and the other in the right basal ganglia. Magnetic resonance imaging (MRI) revealed at least four independent lesions in the right parietal lobe and one lesion in the right basal ganglia (fig. 1). A thoraco-abdominal CT scan revealed no primary tumor. Stereotactic biopsy of one...
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of the parietal lesions showed histopathology suggestive of glioblastoma (World Health Organization [WHO] grade IV). The patient was referred to the oncologists for treatment, and received whole brain radiation therapy (WBRT). Five months after symptom onset the patient experienced worsening of her neurological and clinical condition and ultimately died.

Case 2

A 69-year-old male was admitted with left hemiparesis and ipsilateral central facial nerve palsy with onset day before. His medical history included an ischemic stroke with residual oculomotor palsy, left carotid endarterectomy and an untreated abdominal aortic aneurysm. Brain CT scan revealed three solid lesions, one 5.2 cm in diameter in the corpus callosum, one 3.4 cm in diameter in the right frontal region (in close proximity to the primary motor cortex) and the third, 4.1 cm in diameter in the right tempo-parietal region. MRI showed multiple additional smaller right temporal lesions and one more lesion in the corpus callosum. The patient underwent stereotactic biopsy of the frontal mass. Histopathology revealed grade III (WHO) anaplastic astrocytoma. The clinical condition of the patient allowed for no radiotherapy, due to concurrent morbidities, and the finding of numerous lesions suggested a very poor prognosis. The patient died one month after admission.

Case 3

A 39-year-old female presented with left facial nerve palsy and left hemiparesis (3/5), and a one-month history of abnormal gait, difficulty in standing from the sitting position and moderate left upper limb weakness. MRI showed a heterogeneous tumor (5.2x4.4 cm) in the right parietal region with significant surrounding edema, and a butterfly lesion infiltrating the corpus callosum and expanding into the right hemisphere. Two other masses were detected, situated in the right basal ganglia and the left temporal lobe. The corpus callosum infiltration from the larger right parietal mass was suggested to be the obvious pathway of spread to the left hemisphere. Magnetic resonance spectroscopy (MRS) measured an increased Cho/Cr ratio (3.9), low NAA/Cr ratio (0.07) and low NAA/Cho ratio (0.02). A thoraco-abdominal CT scan was negative for a possible primary tumor. The patient underwent stereotactic biopsy of the right parietal lesion and histopathological examination revealed grade IV (WHO) glioblastoma. The patient presented a severe (catastrophic) hemispheric intracerebral hemorrhage after biopsy sampling and died on the first post-operative day.

Case 4

A 61-year-old female patient with a 10-day history of progressive mild left hemiparesis was diagnosed with multiple brain lesions and was admitted for stereotactic biopsy. The initial brain CT scan showed one hemorrhagic calcified lesion in the right paraventricular region and a second hyperdense mass in the parietal convexity. MRI revealed one gross lesion (4.6 cm in diameter) expanding from the right basal ganglia to the insular cortex, a second lesion 2.1 cm in diameter in the right parietal convexity, and underlying leptomeningeal multifocal infiltration. Stereotactic biopsy was performed on the basal ganglia lesion and histopathological examination revealed grade IV (WHO) glioblastoma. The patient was referred to the oncologists for treatment. She received palliative WBRT and died two months after symptom onset.

DISCUSSION

High-grade gliomas with multiple foci are considered to be malignancies that spread through various pathways,
including commissural fibers or the corpus callosum, and the CSF, and also by local metastasis.\textsuperscript{7} MFHGGs are fairly uncommon entities, with a reported incidence from 2–10% to 16%\textsuperscript{2} of all reported gliomas. Most cases are located supratentorially but lesions can also occur in the posterior fossa, with a reported incidence of less than 4%.\textsuperscript{3} MFHGGs can be categorized by their dissemination characteristics into four different patterns: Type I, leptomeningeal dissemination (Ia: nodular and Ib: diffuse, subgroups); type II, subependymal dissemination; type III, satellite tumor (Ilia: identifiable connection to the classic commissural pathways of dissemination, and IIIb: no such connection); and type IV, mixed.\textsuperscript{4} Multiple foci gliomas can also be divided into early (synchronous foci at diagnosis) or late (asynchronous presentation of multiple foci during treatment).\textsuperscript{5} The molecular background of MFHGGs is not yet fully understood. Cytogenetic and molecular analyses suggest that novel genetic markers are involved in the pathogenesis, with a role of p53 in the progression of malignancy, migration, and growth of these glioblastomas.\textsuperscript{6}

MFHGGs are frequently misdiagnosed and treated as metastatic lesions.\textsuperscript{7} The high signal intensity on unenhanced fluid-attenuated inversion recovery T2-weighted sequence (FLAIR-T2) in addition to the absence of gadolinium-enhancement of the cortex adjacent to the enhancing lesion is more frequently associated to high-grade gliomas.\textsuperscript{8} Magnetic resonance spectroscopy (MRS) can also assist in the differential diagnosis, especially with peritumoral measurement and the possible infiltration of tumor cells into the peritumoral edema.\textsuperscript{9} Histopathological diagnosis is necessary for decisions about appropriate management, and stereotactic biopsy of a brain lesion is a usually safe method for making a definitive diagnosis.\textsuperscript{10}

Regarding treatment options, while the Stupp protocol (radiotherapy and concomitant chemotherapy with temozolomide) is currently the standard of care for glioblastomas, the role of surgery is controversial.\textsuperscript{11} It has been reported that aggressive resection of all lesions resulted in survival comparable with that of patients undergoing surgery for a single lesion.\textsuperscript{11} When assessing the median time to progression and the median survival time, it appears that WBRT has not produced superior results, compared to three-dimensional conformal radiotherapy.\textsuperscript{12} Stereotactic radiotherapy also appears to be well tolerated and efficacious in achieving local control of the disease, and may result in improved overall survival.\textsuperscript{2} The prognosis of these patients is not well documented but their survival is significantly worse than that of patients with solitary glioblastoma.\textsuperscript{13}

In our series of four patients with synchronous presentation of MFHGGs open surgery was not undertaken, because of the extent of the disease and comorbidities. Three of the four patients died shortly after diagnosis (1, 2 and 5 months), having been assessed as unable to even receive the Stupp protocol regimen. One patient died during the day after biopsy, due to massive intracerebral hemorrhage. In three cases, the number of lesions in the CT scan was not in concordance with the subsequent MRI study. All patients with multiple brain lesions should be evaluated with at least an initial MRI scan, followed by stereotactic biopsy for definitive histological diagnosis.\textsuperscript{10,14} We emphasize the biopsy, not only to differentiate multifocal gliomas from brain metastases, but also to expedite possible individualized treatment options.\textsuperscript{14,15} Open surgery should be performed only after careful consideration of all concurrent comorbidities, age and clinical presentation at the time of diagnosis. These highly aggressive lesions have a very poor outcome and pose a dilemma regarding management, since no therapeutic approach has demonstrated significant results in enhancing survival and quality of life.

Ethical statement

This study was conducted in accordance to the ethical standards of the Helsinki Declaration of 1975, as revised in 2000.

ΠΕΡΙΛΗΨΗ

Πολυεστιακά γλοιώματα υψηλού βαθμού κακοήθειας: Κλινική συζήτηση επί πολλαπλών σύγχρονων εστιών

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Τα πολυεστιακά γλοιώματα υψηλού βαθμού κακοήθειας αποτελούν μια ασυνήθιστη κλινική οντότητα που παρουσιάζει ορισμένα αμφισβητούμενα χαρακτηριστικά όσον αφορά στη διαγνωστική και στη θεραπευτική προσέγγιση.
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References


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