Management of Multifocal and Multicentric Gliomas

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KEYWORDS

• Multifocal • Multicentric • Glioma • Glioblastoma
• Treatment

The diffuse nature of gliomas has long confounded attempts at achieving a definitive cure. Superradical hemispherectomies were performed in the early years of neurosurgery; yet even these desperate efforts could not prevent tumor from recurring on the contralateral side. With the advent of computed tomography and magnetic resonance imaging (MRI), it became increasingly apparent that gliomas could have a multifocal or multicentric appearance. Treating these tumors is the summit of an already daunting challenge, because the obstacles that must be surmounted to treat gliomas in general, namely, their heterogeneity, diffuse nature, and ability to insidiously invade normal brain, are more conspicuous in this subset of tumors.

EPIDEMIOLOGY

Malignant gliomas represent the most common primary brain tumor in adults. Median survival of patients with glioblastoma after optimal treatment continues to be less than 15 months.[1] Although most gliomas have been described as solitary lesions, multifocal/multicentric lesions have been described with an incidence ranging from 0.5% to 20%.[2–8] Most of the data available specifically regarding multifocal tumors are in the form of case reports or small series. Chamberlain and colleagues[9] described the radiographic patterns of relapse in 80 patients with glioblastoma multiforme (GBM). At diagnosis, 10% of patients had multifocal or multicentric disease, whereas at first recurrence this proportion increased to 14%. Salvati and colleagues[7] published a series on 25 patients with multicentric tumors and reported that these multicentric tumors represented 2% of all malignant tumors in their series. Silbergeld and colleagues[10] reported that 17% of 117 adult patients with supratentorial GBM examined post mortem by autopsy had multifocal disease.

Multicentric/focal gliomas can either be multiple at the time of diagnosis or develop later in the disease process. Kyritsis and colleagues[11] described 51 patients with multifocal/multicentric gliomas; 26 of the patients had simultaneous lesions at the time of diagnosis, whereas the other 25 developed multifocality later. In 14 of the 51 patients, no apparent dissemination route was identified, and the tumors were classified as multicentric gliomas. The rest of the patients showed different patterns of spread from the primary site, and the tumors were classified as multifocal. The investigators described the meningeal-subarachnoid space as the most frequent dissemination route, followed by the subependymal route, intraventricular route, and direct brain penetration.[11]

DEFINITION: MULTIFOCAL VERSUS MULTICENTRIC TUMORS

Multicentric gliomas were first described by Bradley[12] in 1880. Based on the points brought up by Russell and Rubinstein, Batzdorf and Malamud[2] described the criteria to differentiate multifocal from multicentric tumors in 1963. The investigators described multifocal tumors as those that can be explained as the result of growth or dissemination via established routes: (1) commissural or other

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pathways, such as the corpus callosum; (2) cerebrospinal fluid channels, either through subarachnoid spaces or the ventricular system; and (3) local metastasis through satellite formation in the immediate vicinity of the main tumor. Multicentric tumors were defined as those that represent widely separated lesions, for example, those in different hemispheres and whose origin cannot be explained following the pathways mentioned earlier. Multicentric tumors also include those tumors separated in time.[2] Although these definitions can be used to separate patients with multifocal gliomas from those that harbor multicentric tumors, the clinical or prognostic significance between these 2 clinical entities remains unclear.

PATHOGENESIS

The pathogenesis of multicentric tumors is unknown. In 1960, Willis[13] introduced the theory of initiation and promotion that allows unlinked proliferation of neoplastic cells at different topographic locations[4] and suggested that multicentric lesions could result from a 2-step process. In the first stage called initiation, a large area or perhaps the entire brain undergoes neoplastic transformation and becomes more susceptible to neoplastic growth. In the second stage called promotion, the neoplastic proliferation occurs in multiple sites through different sources of stimulation, such as hormonal, biochemical, or even viral.[14,15] The increased prevalence of multicentric tumors in patients with germline p53 mutations and neurofibromatosis type I (with germline mutation of the *NF1* tumor suppressor gene) is likely explained by the mechanism by which the germline mutation serves as the initiating hit.[16,17] The idea of initiation and promotion also makes sense in the context of the cancer stem cell hypothesis, as elaborated later.

Despite this theory, most cases of multicentric tumors and all cases of multifocal tumors are more likely to develop because of the unique propensity of glioma cells to invade normal brain and migrate long distances. (Claes and colleagues[15] aptly compared glioma cells to guerilla warriors capable of invading individually or in small groups and abusing preexisting supply lines.) In 1940, the neuropathologist Hans-Joachim Scherer[18] described secondary structures of glioma growth along existing cytoarchitectural elements, such as neurons, white matter tracts, and blood vessels. In 1997, Geer and Grossman[19] suggested that interstitial fluid flow along white matter tracts could be a potentially important mechanism for the dissemination of glioma cells, explaining that glioma cells are inherently capable of migration along white matter tracts to distant areas of the brain. Hefti and colleagues[4] found most multicentric glioma lesions to be located along known migrational pathways of glioma cells and, therefore, suggested that active migratory processes are involved in the development of these lesions. The investigators also described a time-related dependency for multicentricity and concluded that with the advent of radical tumor resection, adjuvant therapies, better local control, and longer life expectancy, the incidence of multicentric/multifocal gliomas is likely to increase.

PATHOLOGY

Pathologically, most multicentric/multifocal gliomas can be classified as GBM.[2,7] However, anaplastic astrocytoma, anaplastic oligoastrocytoma, gliosarcoma, oligodendroglioma, and ependymoma with multicentric and multifocal features have been described.[2,7,20] These tumors do not exhibit any specific histologic features that could differentiate them from similar unifocal gliomas.[2] In most cases, the histology of separate lesions is similar, with variations comparable to those visualized in different areas of the same tumor.[2] However, less commonly, multicentricity can also occur as a combination of different histologic tumors, for example, anaplastic astrocytoma and glioblastoma, low-grade astrocytoma and anaplastic astrocytoma, and low-grade astrocytoma and glioblastoma.[5,7,21] Most multicentric gliomas occur supratentorially, but combined lesions in both supratentorial and posterior fossa have also been described.[2,7,8,22,23]

DIAGNOSIS

MRI with contrast is the modality of choice for evaluating brain tumors. Glioblastomas, brain metastases, and central nervous system (CNS) lymphomas share similar enhancement patterns on MRI, and no definitive characteristics can differentiate multifocal/multicentric GBM from metastatic disease or CNS lymphoma.[3,22,24] Very recently, Wang and colleagues[25] reported the use of a combination of MRI diffusion tensor imaging (DTI) and dynamic susceptibility contrast-enhanced (DSC) MRI to differentiate glioblastomas from metastases and lymphoma. Using DTI and DSC parameters, the investigators were able to differentiate GBM from metastases and lymphoma with a sensitivity of 89% and specificity of 93%.

Although important strides are being made to radiographically differentiate between these pathologic conditions, tissue diagnosis with surgical biopsy remains the standard of care for all gliomas including multifocal/multicentric tumors.