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Gliomatosis Cerebri

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ABSTRACT Gliomatosis Cerebri (GC) is a rare tumor of the central nervous system. It is defined as a diffuse glial tumor that extensively infiltrates the brain, involving more than two lobes. And it is listed as a subtype of astrocytic tumors according to the newest 2007 (4th edition) WHO classification of tumors of the Central Nervous System. GC can be subdivided into Type I and Type II. Clinical findings for patients with GC are usually subtle and nonspecific. The lesions of GC generally show hypo, or isodensity on CT; a poorly defined diffuse hypo- or isointense signal on T1-weighted images, and a scattered diffuse hyperintense signal on T2-weighted images. Histological examination of GC reveals widespread infiltration of neoplastic glial cells with minimal destruction of pre-existing structures.

Diagnosis of GC can be ascertained on the basis of a combination of clinical, radiological and pathological data. The treatment of GC includes radiotherapy and chemotherapy; however, the optimal therapeutic strategy is still not well established and prognosis of GC remains poor. This report reviews in detail the aspects of GC mentioned above, and three controversial issues are also discussed in the report.

KEY WORDS: gliomatosis cerebri, stereotactic biopsy, histology, treatment, prognosis

Introduction

Gliomatosis cerebri (GC) is a rare tumor of the central nervous system. It is characterized by diffuse neoplastic infiltration of glial cells in varying stages of differentiation, with the preservation of anatomical architecture and the sparing of neurones. The term "gliomatosis cerebri" was introduced by Nevin in 1938, and about 400 cases have been reported in the literature[1-6].

Definition

In the 1979 World Health Organization (WHO) classification of brain tumors, GC is considered as a undifferentiated and embryonic tumor[7]. In the 1993 and 1999 WHO classifications, GC is defined as a diffuse glial tumor that extensively infiltrates the brain, involving more than two lobes (frequently bilaterally), and occasionally extending to infratentorial structures, or the spine, with the preservation of the structure of the normal surrounding tissues. It is listed as a subgroup of neuroepithelial neoplasm of unknown origin[8,9]. According to the newest 2007 (4th edition) WHO classification of tumors of the Central Nervous System, GC is listed as a subtype of astrocytic tumors[10].

Classification

GC can be subdivided into two forms based on descriptive neuropathologic grounds, Type I and Type II. Type I is a diffusely infiltrating glioma without formation of an obvious tumor mass, whereas Type II denotes the coexistence of a diffuse infiltrating low-grade glioma with associated tumor mass formation, usually showing features of a malignant glioma. Patients who have a solitary mass that later disseminates should not be considered as GC[1,6,11].

Pathogenesis

The pathogenesis of GC is still quite controversial. The widespread nature of GC has led to the formation of two different hypotheses regarding its origin, i.e., *i*) GC arises from simultaneous neoplastic transformation of cells in different regions of the brain (oligoclonal origin hypothesis) or *ii*) GC arises from a single clone of cells and then spreads widely (monoclonal origin hypothesis)[1-3]. Recent genetic analyses have not resolved this problem[12-14].

Clinical manifestations

There is a wide range in age at presentation of GC (a range of 1 month to 85 years)[3,15]. The majority of patients are male (as true in all gliomas) and comparatively young. Artigas et al. [16] described a bimodal distribution of age at initial GC diagnosis, peaking in the second and fifth decades of life. Armstrong et al.[3] observed that 62% of patients with childhood GC were diagnosed in the second decade of life, and the median age at presentation was 12 years, confirming an increase in the incidence of GC during the second decade. The duration of sympotoms before diagnosis was remarkably variable, ranging from 1 week to 22 years[2,3,16].

Clinical findings for patients with GC are usually subtle and nonspecific, mainly determined by the anatomic site involved. Patients most often show an insidiously evolving syndrome comprised of progressive headache, mental status changes, hemiparesis, and seizures (partial with or without secondary generalization). Findings on neurologic examination include evidence of raised intracranial pressure (papilledema, ophthalmoplegia, gait disturbance), neurobehavioral changes, and corticospinal deficits[1,3,4,14].

Vates et al.[1] made a retrospective review of the 22 cases. The most common complaints included mental status changes (77%), seizures (50%) and headaches (41%). The most common neurological manifestations included dementia (68%), corticospinal deficits (36%), gait abnormalities (36%), and papilledema (27%). Taillibert et al.[2] studied the information from 296 cases (90 patients in the French Neuro-Oncology registry database ANOCEF and 206 cases reported in the literature). They observed the usual symptoms including seizures (92 cases), intracranial hypertension (58 cases), changes in mental status (55 cases), or focal neurological deficits (50 cases). Cecocentral scotoma, disorientation, stroke attack, atypical parkinsonian syndrome[17-19], even preudo-subarachnoid and cortical visual impairment also were reported as symptoms of GC[20]. In general, the majority of patients with GC show the same symptoms as patients with low-grade astrocytoma.

Radiographic features

Computerized tomography and magnetic resonance imaging

In general, isodense and hypodense lesions are seen on computerized tomography (CT) with a more or less diffuse mass effect and with no enhancement after intravenous contrast medium administration. However, CT shows only nonspecific diffuse lesions, and sometimes fails to show the condition, or to define its extent accurately[21-24]. Due to its good tissue characterization properties and multiplanar imaging capacity, magnetic resonance imaging (MRI) provides better tissue contrast than CT, so it is more sensitive than CT for detecting lesions and shows the extent of disease better than CT. Generally, a lesion produces a poorly defined diffuse hypo-, or isointense signal on T1-weighted images, and a scattered diffuse hyperintense signal on fluid-attenuated inversion and T2-weighted images. In the infiltrated region, there is an overall increase in volume; sulci are narrowed and gyri swollen. Contrast enhancement is inconsistent. When present, it is usually nodular and minimal, with a minor mass effect, minor perifocal edema and no necrosis. The relative preservation of the blood-brain barrier is thought to be the underlying reason for the inconstant contrast enhancement in GC, and the focal enhancing lesions probably correspond to areas of anaplastic transformation. In the regions of tumoral infiltration, there is an absence of clear delineation between white and gray matter. A mass effect is absent or minimal [1,4,21-24].

Lesions involve more than two lobes. In the study by Peretti-Viton et al.[11], the tumors involved 4 lobes or more (4~8) in 7 cases, while the 2 other tumoral processes involved 3 lobes. A study by Kim et al.[4] of 16 cases showed the extent of involvement was as follows: more than 4 areas in 7 cases, 4 areas in 5 cases, 3 areas in 2 cases, and 2 areas in 2 cases.

The topography of the tumor infiltration is often characteristic, involving mainly the white matter, basal ganglia, thalamus, centrum semiovale, corpus callosum, and less often the hypothalamus; some cases even show involvement of the entire neuraxis. White matter involvement is frequently bilateral but not necessarily symmetric[21-24]. In the study by Peretti-Viton et al.[11], the infiltrative tumoral process involved particularly the

basal ganglia (9 cases), the corpus callosum (8 cases), brainstem (6 cases), and hypothalamus (5 cases). In the study by Kim et al.[4], the basal ganglia and thalami were involved in 9 cases. Enlargement of the corpus callosum was detected in 8 cases and involvement of the brain stem in 7 cases. Brainstem, hypothalamus, centrum semi ovale involvement and spread of the tumor along white matter tracts, such as corticospinal tract, when present, are highly suggestive of GC. However, MRI may underestimate the extent of the tumor, and the changes in MRI are nonspecific. Patients are often misdiagnosed with other neurological diseases such as CNS inflammatory diseases, vasculitis, or leucoencephalopathies.

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) can detect different metabolic levels within brain tissue, and assisted by this information, the normal brain tissue can be differentiated from tumors or other diseases[25-27]. MRS provides a noninvasive biochemical assay of normal and pathologic brain tissue, Many studies have reported increased choline (Cho)/creatine (Cr) and choline (Cho)/N-acetylaspartate (NAA) ratios in tumors as compared with normal brain tissue. Furthermore, the information can reveal tumor progression or recurrence[26,27].

A number of groups have examined the MRS signature of GC. Almost all of them reported elevated Cho/NAA in neoplastic areas compared with normal brain tissue. This information is similar to that derived from common glial tumors, supposedly caused by a decrease of NAA, indicating replacement of neurons by neoplastic glial cells; and an increase of Cho, caused by an increased membrane turnover in tumors[28-35]. This spectroscopic pattern of neoplastic brain lesions may help us distinguish GC from nonneoplastic diseases. Most studies found an increase in the Cho peak, which has been considered as a marker for brain tumors. However, two reports described two cases with histolgically proven GC which showed a normal choline level[33,34]. Guzman-de-Villoria et al.[30] found that there was an inverse relationship between the Cho/Cr ratio and survival time, that may explain the different choline levels measured with MRS in GC.

Moreover, MRS can be of great importance in the grading of GC. The quantitative assessment of Cho/NAA ratios has been used as an aid in the grading of gliomas. Bendszus et al.[31] studied the spectroscopic information of 8 patients with GC, they observed a moderate Cho/NAA ratio increase of up to 1.3 in patients with low-grade lesions, whereas, anaplastic lesions exhibited a distinctly higher Cho/NAA increase of at least 2.5, with the maximum value of 8.9 in a high-grade tumor. Yu et al.[28] also observed that anaplastic lesions had a higher Cho/NAA ratio. The MRS findings in the literature of GC do not agree with the choline level.

Although no specific features that differentiate GC from other glial neoplasm have been observed, MRS may be beneficial in reflecting the true extent of neoplastic infiltration, as compared with conventional imaging techniques. The area of maximum Cho/NAA increase may be used to assess the overall tumor grade, and this targeting information could guide biopsies. MRS can also be used for follow-up examinations.

Positron emission tomography (PET)

Positron emission tomography (PET) is another noninvasive method that is a valuable tool in the elucidation of GC. A few studies that describe PET findings in GC using different tracers have been reported[36-39]. Dexter et al.[38] using 2-^{18}F-2-deoxy-D-glucose (FDG) PET, demonstrated tumor-associated cortical suppression of glucose metabolism in areas of involvement in a single patient with GC. However, decreased uptake of FDG is nonspecific and also observed in other diseases such as infection, diffuse ischemia and demyelinating diseases. Mineura et al.[37] performed PET with ^{11}C-L-methionine in a 32-year-old woman with extensive tumor infiltration of gray and white matter of both temporooccipital lobes. They found that ^{11}C-methionine-PET was better able to delincate the extent of the tumor when compared with MRI. Shintani et al.[36] demonstrated that serial PET may be used to evaluate the extent of GC. Sato et al.[39] examined 8 patients who had GC and 6 patients who had nonneoplastic disease with L-^{18}F-α-methyl tyrosine (FMT) PET and FDG PET. They observed significant differences between the standardized uptake (SUV) of FMT and the tumor-to-normal cortex (T/N) ratio of FMT in GC and in the controls, and between the T/N ratio of FMT and FDG in GC. Those results demonstrated that increased uptake of FMT PET strongly suggests a neoplasm, and FMT PET can provide better high-contrast PET images than FDG PET. They pointed out that FMT PET was valuable for differentiating GC from nonneoplastic diseases. However, these preliminary studies only involved single or a small series of cases, and further investigation with larger samples will be need to clarify the usefulness of PET in diagnosis, grading, and follow-up examinations for GC.

Pathology

Histological examination of GC reveals the widespread infiltration of neoplastic glial cells with minimal destruction of pre-existing structures, and frequently a preferential infiltration of the white matter. In the affected white matter, neoplastic cells are often arranged parallel to the fiber tracts, and myelin sheaths may be destroyed, but axons are only slightly or even not destroyed. Perineuronal, perivascular, and subpial spread of tumor infiltration can be observed. There is an absence of demarcation between normal and affected areas. Areas of high mitotic activity and microvascular proliferation may be observed, and secondary malignant tumor areas can arise

at different sites within the previous low-grade tumor, but necrosis is rare [1-4,11].

The neoplastic glial cells consist of different degrees of maturation (ranging from Grade I to Grade IV, predominately low-grade). Tumors with multiple grades may coexistence in an individual. The cellular morphology is variable, most are astrocytic, others oligodendroglial, and others can be mixed or unclassified[1-6,40]. In the series of Peretti-Viton et al.[11] there were 2 cases of oligodendroglioma, 1 case of anaplastic oligodendroglioma, 2 cases of anaplastic mixed oligoastrocytoma, 1 case of anaplastic astrocytoma, 2 cases of glioblastoma and 1 case of astrocytic proliferation. In the study by Taillibert et al.[2] , tumors were identified as astrocytic in 108 cases, oligodendroglial in 54 cases, mixed in 17 cases, with 117 cases classified as undetermined or non-specified.

Diagnosis and differential diagnosis

Before 1986, pathological diagnosis of GC was based on autopsy data. The first antemortem diagnosis was reported by Troost et al.[41] in 1986 on the basis of MRI and biopsy results. Since then, in the English literature, close to 180 cases received intravitam pathological diagnosis based on biopsy, and of those cases, about 40 patients underwent a stereotactic biopsy[1-6,14-18,42]. In the Chinese literature, there have been nearly 210 cases which received an intravitam pathological diagnosis, and about 30 patients underwent a stereotactic biopsy[43-51].

When patients have symptoms such as headache, personality changes, or focal neurological deficits, and when neuroimaging provides MRI evidence of a diffuse infiltrative process involving more than two cerebral lobes often extending to infratentorial structures, a diagnosis of GC should be considered. But it must be kept in mind that GC may be misinterpreted not only as an ischemic, or infectious disease, but also as a demyelinating disease such as leukoencephalopathy or multiple scerosis. Their changes on CT and MRI images are similar to GC. Other tumor entities, such as diffusely infiltrating astrocytomas and multicentric gliomas, must be considered in the differential diagnosis as well[4,11].

Imaging features of MRS (a "neoplastic" spectral pattern of elevated Cho/NAA) and PET may be helpful to distinguish GC from non-neoplastic diseases[25-27,36-39]. Additionallaboratory findings are helpful in excluding infectious or inflammatory diseases. The acute onset of clinical symptoms in ischemia plays a determing role in differentiating GC from ischemic disorders. The differential diagnosis of leukoencephalopathy is uncommon if the deep or superficial gray matter is involved. The large plaques in multiple sclerosis are usually more circumscribed than changes in GC[10]. When non-tumoral white matter diseases are excluded, multicentric gliomas should be considered[52-54]. Multicentric gliomas consist of scattered neoplastic foci with no detectable microscopic continuity between them. The MRI characteristics of multicentric gliomas are different from those of GC. In multicentric gliomas, tumor masses occur at different sites with strong contrast enhancement (often either heterogeneous or ring-like). Centro-tumoral necrosis, perifocal vasogenic edema, mass effect on ventricles and sulci, and centrifugal extension that follows white matter tracts often can be observed. The most conflicting differential diagnosis includes low and high-grade diffuse astrocytomas and oligodendrogliomas. These tumors differ from GC in that astrocytomas and oligodendrogliomas are usually limited tumors, supratentorial, with an "all in one piece" extension. The brainstem is rarely involved in those cases except when the tumor arising from basal ganglia follows the cortico-spinal tract and thus infiltrates the brainstem. Also the hypothalamus is rarely involved. The clinical symptomatology predominately includes seizures in low-grade gliomas and focal deficits in high-grade gliomas[11]. Because gliomas are not sharply delineated tumors, the differences between GC, diffuse astrocytomas, glioblastoma multiforme and oligodendrogliomas are ambiguous.

However, the diagnosis of GC should be confirmed by a histopathological examination. Stereotactic biopsy has evolved as a powerful and safe method to provide a tissue diagnosis with minimal disruption of normal brain function. It plays a significant role in the management of malignant brain tumors. Many other authors have pointed out that stereotactic biopsy is preferred over surgical biopsy in the diagnosis of cranial lesions. In comparing common open biopsies with the stereotactic method, the following advantages are noted: only a small hole is made in the skull (no trepanation), deep targets can be easily reached without significant brain damage, the precise location of the biopsy can be achieved, and multiple biopsies can be taken at intervals along one or several tracks in order to determine the various aspects of the lesions in respect to size, limits, anaplastic foci, and local variations, etc.[55,56] Thus far, about 40 cases with GC have been pathologically confirmed through stereotactic biopsy. In the study by Peretti-Viton et al.[11], the pathological data were obtained by stereotactic biopsy in 4 cases, and by surgical biopsy in 5 cases. In the study by Taillibert et al.[2], 12 patients underwent stereotactic biopsy, compared to 5 patients who underwent open biopsy. No statistical analyses comparing surgical biopsy with stereotactic biopsy in GC have been reported. The advantages of stereotactic biopsy may also apply for the pathological diagnosis of GC.

A definite diagnosis of GC should be arrived at on the basis of a combination of clinical, radiological and pathological data. However, there have been no precise diagnotic criteria established for GC, and the differences between GC, diffuse astrocytomas, glioblastoma multiforme and oligodendrogliomas remains unclear. Therefore, valid diagnosis criteria should be established and

further studies focusing on the difference between GC and common gliomas should be performed. We recommend the criteria proposed by Peretti-Viton et al.[11], that is MRI evidence of a diffuse tumor infiltration in the brain (with or without small enhancing nodules) consistent with the WHO definition of GC (a diffuse tumor with extensive infiltration of more than two lobes of the brain, frequently bilateral, and often extending to basal ganglia, thalamus, corpus callosum, brain stem, hypothalamus and spinal cord).There should be confirmation of astrocytic or oligodendrocytic proliferation by biopsy according to the WHO classification of tumors. That may be helpful in making a diagnosis of GC in clinical work.

Therapy

Although there has been considerable progress in the initiation of clinical trials to establish treatment regimes specifically designed for GC, an optimal therapeutic strategy is still not well established. Most studies argue that surgery is not a viable option because there is widespread dissemination of neoplastic glia. It is limited mainly for primary biopsy and determination of tumor histology. However, Zheng et al.[49] and Zhang et al.[50] propose that surgery is an optional therapy for GC, and the degree of operational incision is an important factor affecting the prognosis.

Radiotherapy may be useful. Brain irradiation can stabilize or improve neurologic function. In 4 published retrospective studies[4,57-59], 58% (24/41) of evaluable patients had a clinical response, and 31% (13/41) had a radiologic response, with a median survival time ranging from 11 to 38 months. The optimal configuration of the radiation field cannot be determined at present, but extensive involved-field therapy, or whole-brain radiotherapy (WBRT) appears to be the most appropriate forms of radiotherapy for most patients. However, large field or whole brain radiotherapy may carry considerable risk of severe delayed toxicity such as delayed leukoencephalopathy, which was reported in 28% and 12% of patients, respectively, in a large retrospective study [60].

Chemotherapy represents another alternative therapy regimen. Beside some reports about the value of temozolomide (TMZ) treatment in individual cases, 2 larger prospective studies have recently established that a significant proportion of patients will benefit from an initial chemotherapy treatment with PCV (procarbazine, lomustine, vincristine), or TMZ. Sanson et al.[61] treated 63 consecutive GC patients with initial chemotherapy consisting of either PCV (procarbazine, 60 mg/m^2 on days 8 to 21; CCNU, 110 mg/m^2 on day 1; and vincristine, 1.4 mg/m^2 on days 8 and 29), or temozolomide (TMZ; 150 to 200 mg/m^2 for 5 days every 4 weeks). Seventeen patients received 1 to 6 cycles (median, 5) of PCV, and 46 received 2 to 24 courses (median, 13) of TMZ. Clinical objective responses were observed in 21 of 63 (33%) patients, and radiologic responses were seen in 16 of 62 (26%). Overall survival of patients treated with either therapy was 29 months, with no statistical differences between the two groups. However, in the study, there were 14 cases which presented as a circumscribed glioma at onset, and later spread in a diffuse manner. Those cases cannot strictly be classified as GC according the WHO classification, so treatment in this group may not be fully applicable to other dense GC. In the study of Levin et al.[62], 11 radiotherapy patients who had not received prior radiotherapy received a median number of 10 treatment cycles of TMZ. A positive response was noted in 5 patients (45%), and the median time to tumor progression was 13 months with a progression-free survival of 55% at 12 months. Interestingly, it was found that there was high proportion of oligodendroglial tumors in the two studies, and oligodendroglial tumors are known to be chemosensitive. The inherent sensitivity of oligodendroglial tumors was elegantly shown to have a molecular correlation (i.e., 1p or 19q chromosomal loss).

It is important to select the most appropriate treatment (or combination) according to the tumor characteristics. Because it is necessary, in general to limit the neurotoxicity of large-field radiotherapy when treating a wide-spread infiltrative tumor, the current approach is to treat GC, in particular oligodendroglioma, with primary chemotherapy. The choice of a primary chemotherapy regimen for GC includes PCV and TMZ, the latter demonstrating similar efficacy with reduced toxicity. If the disease progresses despite first-line chemotherapy, 25% to 50% of the patients can be expected to respond to second-line chemotherapy (most often with one of the above 2 regimens not previously used). When tumors progress despite first and second-line chemotherapy, radiotherapy should be used as a salvage therapy [13,15].

Prognosis

Despite aggressive and often multimodal therapeutic intervention, prognosis of GC is still poor[1-11,13,15]. Of the 22 cases reported by Vates et al.[1], the median length of survival was as follows: no treatment, 1 month (n = 4); radiotherapy alone, 28 months (95% confidence interval, 5~51 months; n = 13); radiotherapy followed by chemotherapy, 2 patients, alive at 28 and 104 months; radiotherapy and chemotherapy simultaneously, 3 patients, one alive at 18 months and the others died at 7 and 9 months. In the study by Taillibert et al.[2] analyzing 296 individual cases, the median survival time (MST) was 14.5 months. In the study by Herrlinger et al.[6], the MST was 14 months (ranging from 4~91 months) after detection of T2 hyperintensities by MRI indicating for GC, and 16 months after histological diagnosis (ranging from 2 to 96 months). Armstrong et al.[3] studied 13 pediatric

patients who were diagnosed as GC and were treated at the Children's Hospital of Philadelphia. They found the overall survival rate was 64% after 2 years (range, 6.5 to 67 months).

There are perhaps, some factors which may effect the length of survival. Vates et al.[1] found that the Karnofsky Performance Scale scores and grade were directly related to length of survival. In the study by Taillibert et al.[2], the MST was higher for patients with a performance status ≥ 80 (27 months *vs.* 9 months), low grade gliomatosis (Grade II = 20 months, Grade III = 11.5 months, Grade IV = 8.5 months), oligodendroglial subtype (36 months compared to 14 months for mixed GC and 11 months for astrocytic GC). Kim et al.[4] pointed out that a Ki-67 labelling index greater than 1.0 had a significantly unfavourable impact on survival. In their series, the MST and one-year survival rates of the 6 patients with a Ki-67 labelling index greater than 1.0 were 9 months and 37.5%, whereas no deaths occurred among the 5 patients whose labeling index was 1.0 or less. Armstrong et al.[3] found that an age of < 10 years and contrast enhancement on MRI at diagnosis may be risk factors indicating a shorter survival in pediatric patients with GC.

Controversial issues

Does a GC represent a separate entity, or rather a subset of common glial neoplasms?

Although a GC usually demonstrates histomorphological features of a low-grade tumor, the formation of secondary highly malignant tumor regions may occur. Occasionally, GC cases with focal or pure oligodendroglial appearance have been reported. This raises a question as to whether GC represents a separate entity or rather merely a highly infiltrative subtype of common glial neoplasms. One reasonable way to answer this question regarding the cell of origin in GC would be an analysis of GC tissue for molecular alterations commonly found in other astrocytic tumors.

One of the most commonly altered tumor suppressor genes in human cancer is TP53. TP53 gene alterations occur in about 30%~50% of astrocytic gilomas, and it has been suggested that TP53 alterations represent an early event in astrocytic tumor formation. The younger patients diagnosed with a low-grade astrocytoma frequently show TP53 alterations, and they may undergo tumor progression to anaplastic astrocytomas and secondary glioblastoma multiforme (GBM). TP53 mutations are infrequent in older patients having de novo GBM[63,64].

An indication of impairment of p53 function in tumor is given by the detection of nuclear p53 accumulation. Nuclear p53 immunoreactivity has been reported to be present in both low-grade and high-grade tumor areas in GC, but the frequency is variable. Two reports found p53 expression present in 36% (4/11)[4] and 50% (9/18)[65] of cases, respectively, while another study reported 6 out of 8 (75%) cases to be p53 positive[6]. Mutation of TP53 has also been found in GC, but the frequency seems to be lower compared to other common astrocytomas, and there is some degree of regional heterogeneity.

Other genetic alterations which frequently occur in primary de novo glioblastoma, and not in low grade gliomas, are related to the genes such as epidermal growth factor receptor (EGFR), murine double-minute 2 (MDM2), CDKN2A (p16), PTEN (phosphatase and tensin homolog deleted on chromosome 10) and the retinoblastoma gene (Rb). So far, no significant molecular genetic alterations in any of these genes have been reported [12-14,65-67].

Summarizing the molecular genetic and immunohistochemical data, it is clear that the most frequent molecular genetic alteration in GC is TP53. The presence of TP53 alterations in some low-grade tumor areas might be the basis of genetic instabilities, leading to yet-unidentified secondary molecular aberrations responsible for the mode of GC tumor spread. It is also possible that in GCType I, the same alterations (TP53) are present early on, but the additional ''hit'' is missing to induce a secondary progression as seen in GC Type II. And we still have not identified one or more unique molecular alterations in GC, meaning that mostly likely GC represents a subform of a common astrocytoma. All these molecular findings strongly support the notion that GC is a subtype of a common glioma. So in the newest 2007 WHO classification of tumors of the Central Nervous System, GC is listed as a subtype of astrocytic tumors [12-14].

Is the origin of GC monoclonal or polyclonal?

With respect to a large tumor involvement of the brain at diagnosis, it is unclear if the process started in a circumscribed area and subsequently spread, or if the tumor process has had a multifocal origin. This raises the important question: did one single tumor clone spread through the brain (i.e., a monoclonal origin), or are multiple genetic events at different sites at different times which lead to the formation of separate tumor clones with distinct histopathological features (i.e., a polyclonal origin). Thus far, there are only limited data available on this issue.

The study by Hecht et al.[68] demonstrated 2 distinct karyotypes in the single GC case, differing only in the ploidy grade, but not in chromosomal rearrangements. This observation is compatible with a monoclonal origin of GC. Kirches et al.[69] analyzed the length variability of a noncoding polycytosine tract (hypervariable region, HVR2) of mitochondrial DNA (mtDNA) from various tumor sites of GC patients[12]. They found 2 male patients with identical allelic losses either in all tumor areas (suggesting monoclonality), or in those of one hemisphere. The result in the latter patient proved a common origin of all tumor cells in one hemisphere, and was at

least compatible with true monoclonality.

Additional strong evidence for a monoclonal origin of GC and a further proof of the enormous infiltrative power came from a case study by Kros et al.[24] They reported an identical TP53 mutation in various widely separated tumor regions (left and right hemisphere) showing features of a low-grade astrocytoma. Additionally, in this case they identified chromosome 2q11-q31 losses in 13 of 24 samples, and chromosome19q13-qter losses in 10 of 24 samples from both left and right hemispheres by means of comparative genomic hybridization (CGH). Until now, evidence for a polyclonal origin has not been convincingly reported.

Taken together, the few reports provide better evidence for a monoclonal origin of most GC cases. Most importantly, however, single transformed GC cells are surely able to proliferate into a cell clone infiltrating large and extremely distant brain areas initially without major tissue destruction.

What determines the highly infiltrative multilobar nature of GC cells?

Assuming that GC orginates from the expansion of a single tumor cell clone, the question concerning the phenotypic differences responsible for the extraordinary spread of the tumor cells compared to other gliomas must be addressed. Invasion of common malignant astrocytomas is known to occur as a composite process of increased expression of factors degrading components of the extracellular matrix (ECM), growth factor overexpression, increased migratory potential, as well as expression of receptors favoring cell molitily. To further elucidate the specific characteristics of the tumor cells in GC that enable them to infiltrate extraordinary large parts of the brain, many studies analyzed specific factors supporting cell motility and migration in GC patients (Table 1).

Table 1. Assessment of tumor cell invasion factors in GC.

	Author	Year	Cases	Positive rate (%)
MMP-2	Kunishio[75]	2003	3	100 (3/3)
MMP-9	Kunishio[75]	2003	3	67 (2/3)
	Mawrin C[71]	2005	9	0
Tenascin-C	Mawrin C[71]	2005	9	100 (2/3)
CD44	Mawrin C[71]	2005	9	66 (6/9)
L1	Suzuki[76]	2005	4	100 (4/4)

Tenascin C (TN-C), a large ECM glycoprotein, was first described as a tumor-specific antigen. It is expressed in a high percentage of malignant glioma cell lines and GBM samples, but not in low-grade astrocytomas and normal brain samples. TN-C expression has been found to be enhanced in basement membranes of glomeruloid endothelial proliferations in GBM. The migration rate of malignant glioma cells is higher on TN-C monolayers compared to collagen, fibronectin, or vitronectin layers[70]. These data suggest a critical role for TN-C in glioma cell motility and cell migration. In GC, TN-C expression was found in only 3 cases (33%) from the study by Mawrin et al.[71] In these cases, there was not an obvious relationship with the grade of tumor cells.

CD44 supports attachment of tumor cells to hyaluronate, one of the most abundant components of the extracellular matrix (ECM) in the brain. CD44 has been proposed as a brain invasion marker for GBM in a study comparing CD44 expression in glioblastoma versus meningioma[72]. Another study found a tendency towards increased CD44 expression in high-grade gliomas[73]; on the other hand, 2 other studies[70,74] did not find differential CD44 expression in low versus high-grade astrocytomas. Mawrin et al.[71] found CD44 expression in 6 out of 9 cases, which may suggest that CD44 is involved in GC tumor cell migration.

Matrix metalloproteinases (MMPs) are proteolytic enzymes contributing to degradation of protein, regulation of cancer cell growth, differentiation, migration, and invasion. MMP-2 and MMP-9 represents the most abundant MMP found in gliomas. A study by Kunishio et al.[75] reported a strong expression of MMP-2 in all of 3 GC cases and of MMP-9 in 2 of them. The expression scores for MMP-2 and MMP-9 tended to be higher in GC compared to diffuse astrocytomas, anaplastic astrocytomas, and GBMs investigated simultaneously in the study. However, Mawrin et al.[71] failed to detect MMP-9 immunoexpression in their recent autopsy series.

The L1 molecule (L1 cell adhesion molecule), plays an important role not only in neurone-neurone adhesion but also in nerite fasciculation, neurite outgrowth on Schwann cells, and neural cell migration. Suzuki et al.[76] postulated that L1 plays an important role in the migration of glioma cells via homophilic binding, when they carried out an immunohistochemical analysis of neoplastic cells from 4 patients with GC and 20 with astrocytic tumors using antibodies against GFAP and L1. They found patients with GC strongly expressed glial fibrillary acidic protein and neural cell adhesion molecule L1, whereas patients with other types of glioma expressed L1 only weakly. The results suggest that L1 expression may play a role in the spread of GC.

Taken together, the data show that widespread infiltration of large parts of the brain in GC seems be associated with a certain expression pattern of infiltration-favoring factors such as CD44, TN-C, MMP-9 and L1. However, the relationship is not definitive at the present time.

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