Giant cell glioblastoma

A rare variant Glioblastoma IDH wildtype comprising <1% of glioblastomas. Histology features bizarre, multinucleated giant cells and, in some cases, abundant reticulin network. Tends to develop in younger patients (mean age = 51 years) than IDH-wildtype GBM (62 years). As with IDH-wildtype GBM, these tumors appear to arise de novo with no known precursor.

The giant-cell glioblastoma is a histological variant of glioblastoma, presenting a prevalence of bizarre, multinucleated (more than 20 nuclei) giant (up to 400 µm diameter) cells.

It occasionally shows an abundant stromal reticulin network and presents a high frequency of TP53 gene mutations.

Symptoms and signs are similar to those of the ordinary glioblastoma. Methodology of diagnosis and treatment are the same.

The giant-cell glioblastoma was originally termed “monstrocellular sarcoma”, because of its stromal reticulin network, but the astrocytic nature of the tumor was firmly established through the consistent GFAP expression analysis.

The giant-cell glioblastoma is a rare neoplasia: its incidence is less than 1% of all brain tumors. It represents up to 5% of glioblastomas.

The mean age at clinical presentation is 42. The age distribution includes children and has a wider range than other diffuse astrocytomas (diffuse WHO grade II astrocytoma, anaplastic astrocytoma, ordinary glioblastoma). The giant-cell glioblastoma affects males more frequently. (The M/F ratio is 1.6.)

Most patients with giant-cell glioblastoma have unfavourable prognosis, but some authors report clinical results slightly better than the ordinary glioblastoma, in all probability because this variant seems less infiltrative, due to the nature of giant cells of this type.

Latino Americans are a rapidly growing ethnic group in the United States but studies of glioblastoma in this population are limited.

Shabihkhani et al., have evaluated characteristics of 21,184 glioblastoma patients from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. This SEER data from 2001 to 2011 draws from 28% of the U.S.

Latinos have a lower incidence of GBM and present slightly younger than non-Latino Whites. Cubans present at an older age than other Latino sub-populations. Latinos have a higher incidence of giant cell glioblastoma than non-Latino Whites while the incidence of gliosarcoma is similar. Despite lower rates of radiation therapy and greater rates of sub-total resection than non-Latino Whites, Latinos have better 1 and 5 year survival rates. SEER does not record chemotherapy data. Survivals of Latino sub-populations are similar with each other. Age, extent of resection, and the use of radiation therapy are associated with improved survival but none of these variables are sufficient in a multivariate

analysis to explain the improved survival of Latinos relative to non-Latino Whites. As molecular data is not available in SEER records, they studied the MGMT and IDH status of 571 patients from a UCLA database. MGMT methylation and IDH1 mutation rates are not statistically significantly different between non-Latino Whites and Latinos. For UCLA patients with available information, chemotherapy and radiation rates are similar for non-Latino White and Latino patients, but the latter have lower rates of gross total resection and present at a younger age [1)].

Differential diagnosis

Giant Cell Glioblastoma (gcGBM) and Pleomorphic Xanthoastrocytoma (PXA) are rare astroglial tumors of the central nervous system. Although they share certain histomorphological and immunohistochemical features, they are characterized by different clinical behavior and prognosis. Nevertheless, few cases remain uncertain, as their histomorphological hallmarks and immunophenotypes do correspond to the typical pattern neither of gcGBM nor PXA. Therefore, in addition to the routinely used diagnostic histochemical and immunohistochemical markers like Gömöri, p53 and CD34, we analyzed if genetic variations like MGMT promoter methylation, mutations in the IDH1/2 genes, or BRAF mutations, which are actually used as diagnostic, prognostic and predictive molecular markers in anaplastic glial tumors, could be helpful in the differential diagnostic of both tumor entities. We analyzed 34 gcGBM and 20 PXA for genetic variations in the above-named genes and found distinct distributions between both groups. MGMT promoter hypermethylation was observed in 3 out of 20 PXA compared to 14 out of 34 gcGBM (15% vs. 41.2%, p-value 0.09). BRAF V600E mutations were detected in 50% of the PXA but not in any of the gcGBM (50% vs. 0%, p-value < 0.001). IDH1 R132 and IDH R172 mutations were not present in any of the PXA and gcGBM cases. Our data indicate, that in addition to the histological and immunohistochemical evaluation, investigation of MGMT promoter methylation and in particular BRAF V600E mutations represent reliable additional tools to sustain differentiation of gcGBM from PXA on a molecular basis. Based on these data specific BRAF kinase inhibitors could represent a promising agent in the therapy of PXA and their use should be emphasized [2)].

Mutations

Due to the rarity of the cases, there has been no comprehensive molecular analysis of gcGBM. Previously, single gene study identified genetic changes in TP53, PTEN, TERT promoter mutation in gcGBM. In this report, we performed whole-exome sequencing (WES) to identify somatically acquired mutations and copy number variations (CNVs) in 10 gcGBM genomes. We also examined TERT promoter mutation and MGMT methylation in our cohort. On top of the reported mutations, WES revealed ATRX, PIK3R1, RB1, and, SETD2 as the recurrent mutations in gcGBM. Notably, one tumor harbored a mutation in MutS homolog 6 (MSH6) that is a key mismatch repair (MMR) gene. This tumor demonstrated hypermutation phenotype and showed an increased number of somatic mutations. TERT promoter mutation and MGMT methylation were observed in 20% and 40% of our samples respectively. In conclusion, we described relevant mutation profiling for developing future targeted therapies in gcGBM [3)].

Treatment

It is recognized that maximum safe resection treatment and adjuvant radiotherapy can improve survival rate (5-13 months) similar to GBM patients [4)].

Outcome

Patients diagnosed with GC from 1988 through 2004 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. Outcomes were examined with Kaplan-Meier survival analysis and Cox models. For comparison, similar analyses were conducted for patients diagnosed with GBM. GC was identified in 1% of 16,430 patients diagnosed with either GC or GBM. Compared with GBM, GC showed similar gender and racial distributions. Likewise, tumor size and location were not significantly different between the two histologies. GC tended to occur in younger patients with a median age at diagnosis of 51 years, compared with 62 years for GBM. Additionally, patients with GC were more likely to undergo complete resection compared with patients with GBM. For both histologies, young age, tumor size, extent of resection, and the use of adjuvant radiation therapy (RT) were associated with improved survival. Cox modeling suggests the prognosis for GC is significantly superior to that for GBM (hazard ratio = 0.76; 95% confidence interval, 0.59-0.97) even after adjustment for factors affecting survival. GC is an uncommon GBM subtype that tends to occur in younger patients. Prospective data defining optimal treatment for GC are unavailable; however, these retrospective findings suggest that resection, as opposed to biopsy only, and adjuvant RT may improve survival. The prognosis of GC is superior to that of GBM, and long-term survival is possible, suggesting aggressive therapy is warranted [5].

Case series

Oh et al., presented the experience in managing GCG tumors at the University of California, San Francisco. Patients were retrospectively identified through chart review, and data pertaining to patient demographics, treatment plans, and follow-up were extracted from existing medical records. Overall survival (OS) and progression-free survival (PFS) were the primary and secondary endpoints, respectively. In sum, we identified 22 patients who were managed or followed for GCG. Most patients (78%) initially underwent subtotal resection as primary treatment for their tumor, and most also received post-operative adjuvant therapy (90%), with radiation being the most frequently administered modality (85%). Within this institutional cohort, median OS and PFS were 15.4 months and 5.7 months, respectively. On multivariate survival analysis, age (p=0.84), sex (p=0.05), and adjuvant radiation plus temozolomide (p=0.12) were not associated with prolonged OS. However, adjuvant radiation plus temozolomide was associated with longer PFS (p=0.01), and patients receiving this therapy demonstrated a median PFS of 32.9 months versus 13.1 months. These findings confirm the comparatively improved prognosis of GCG over GBM. Moreover, they suggest that extent of resection may not significantly delay recurrence or extend survival, and that combination radiation with temozolomide may represent the optimum adjuvant paradigm to delay tumor progression [6].

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