http://dx.doi.org/10.5272/jimab.2014202.502

Journal of IMAB
ISSN: 1312-773X (Online)
http://www.journal-imab-bg.org

Journal of IMAB - *Annual Proceeding (Scientific Papers)* 2014, vol. 20, issue 2

MULTIFOCAL GLIOBLASTOMA MULTIFORME PRECEDED BY A GEMISTOCYTIC ASTROCYTOMA AND DYSREGULATED IMMUNE RESPONSE

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ABSTRACT:

Glioblastoma multiforme (GBM) is known to be the most common malignant form of astroglial brain tumors. The etiology, cellular and molecular pathogenic mechanisms remain unclear to a great extent. Recent research indicates the role of the immune system in malignant glioma and especially in triggering the mechanisms of local resistance and systemic immune suppression. There is accumulating evidence that the concept of the CNS as an immune-privileged organ is no longer valid. Recent advances demonstrate that it is an immunologically active site, with complex immune responses mostly based on innate immune processes.

Multifocal gliomas with varying histopathological appearance are extremely rare. We report the only case of GBM preceded by a gemistocytic astrocytoma with a very short survival time of just 3 months after the onset of complaints. Interestingly, a normal CD4/CD8 ratio but prominent change in the regulatory T cell lineage was recorded. The elevation of the suppressor CD8+CD11b+ cells and the reduction of cytotoxic CD8+CD11b- cells indicate the prevalence of a suppressor phenotype which provides an explanation for the occurrence of the second malignant tumor, the rapid tumor progression and fatal outcome.

Key words: Multifocal gliomas, gemistocytic astrocytoma, immune response

INTRODUCTION

Glioblastoma multiforme (GBM) is known to be the most common malignant form of astroglial brain tumors and represents about 40% of all primary tumors of the CNS. Despite the combination of modern therapeutic approaches as immunotherapy and novel cytostatic drugs combined with radical surgical resection and radiotherapy, the median survival time is still 14 months after diagnosis. The etiology, cellular and molecular pathogenic mechanisms remain unclear to a great extent. Cerebral traumatic accidents, electromagnetic radiation, alimentary carcinogens, human cytomegaloviruses and gene alterations are suspected.

Recent research indicates the role of the immune system in malignant glioma and especially in triggering the mechanisms of local resistance and systemic immune suppression [1]. A considerable inhibition of cellular immune response has been demonstrated in patients with intracranial tumors [2].

Multifocal gliomas with varying histopathological picture are extremely rare. We report a case of glioblastoma multiforme preceded by a gemistocytic astrocytoma in the opposite hemisphere and preoperatively dysregulated peripheral immune response with prevalence of an immune suppressive phenotype. A very short survival time of 3 months after the onset of symptoms was recorded.

CASE REPORT

A 57-year old woman presented with headache, poor memory and muscle weakness in left extremities for 10 days. On examination, symptoms of increased intracranial pressure (ICP), left hemiparesis and moderate arterial hypertension (B.P. 140/90 mmHg) were detected. At hospitalization the Karnofsky Performance Scale score was estimated as 80. She has undergone surgery for a myomatous polyp 17 years ago and had no family history for malignancies and immune disorders. The cranial computed tomography (CT) showed a large intraparenchymal

lesion in the right frontal region. It was irregularly labeled by the contrast medium. A perifocal edema, compression and dislocation of medial cerebral structures were registered (Figure 1A).

The preoperative laboratory investigation revealed a slightly increased absolute number of WBC (12.21 x 109/L) with significantly decreased lymphocytes (2.7%) and relatively elevated polymorphonuclear neutrophils (91,3%) on differential count. The multicolor flowcytometric immunophenotyping showed a complete dysregulation of both Th1 and Th2 immune response. Interestingly, only the CD3-CD56+ and the CD3+CD56+ populations, representing the NK-cells and NKT-cells respectively, were within the reference range. The increased value of CD19+ cells indicated a shift towards a Th2 immune response. The Th1 immunity was also altered as CD3+, CD3+CD4+ and CD3+CD8+ cell populations were considerably diminished, but the CD4/CD8 ratio stayed normal. The most notable change was registered in the regulatory T cell lineage. The suppressor CD8+CD11b+ cells were elevated – 21.3 (normal range 6.5-16.5), while the cytotoxic CD8+CD11b- cells were lowered – 11.6 (normal range 14-26).

A subtotal resection of the tumor was performed. No additional neurological deficiency occurred. Clinical improvement was recorded. The histopathological examination proved a gemistocytic grade II astrocytoma (Figure 2A). The diagnosis was verified by immunohistochemical detection of glial fibrillary acidic protein (GFAP) (Figure 2B). A normal postoperative period followed till the third week after the operation. Then complaints of progressive headache, somnolence, and muscular weakness in upper and lower extremities developed. The patient did not receive any radiotherapy or chemotherapy during that period. Neurological examination revealed increased ICP, quadriparetic symptoms (more evident for left extremities) and aphasic disorders. Cerebral CT and magnetic resonance imaging (MRI) showed a residual tumor in the operative area spreading to corpus callosum, cystic transformation and development of a second heterointense intraaxial lesion in the left frontal region (Figure 1B). The contrast-enhanced image disclosed a peripheral staining of the tumor with perilessional edema and compression of adjacent brain structures (Figure 1C, D). A further surgical intervention with total resection of the tumor in the left frontal area was carried out. A glioblastoma multiforme with necrotic foci was confirmed on histology. During the second postoperative period no significant clinical improvement was recorded. The patient presented several epileptic seizures, the quantitative disturbances of consciousness deteriorated and a lethal outcome followed 3 months after the onset of complaints.

DISCUSSION

In our patient, the first brain tumor diagnosed was a gemistocytic grade II astrocytoma. This malignancy is still enigmatic and it is not clear if that morphology results in a more aggressive biology compared to other grade II astrocytomas [3] . GBM often occurs in the supratentorial white matter including the corpus callosum. The multifocal localization is not so common, the occurrence of leptomeningeal metastasis and distant metastases is exceptional. A Japanese study describes a case of gemistocytic astrocytoma with subsequent development of an anaplastic astrocytoma in the opposite hemisphere [4]. A gemistocytic astrocytoma with succeeding appearance of a GBM is an extremely rare finding and to our knowledge there is no published evidence for that. In our case the aggressiveness and fast occurrence of a second tumor (GBM) in the opposite hemisphere could be at least partially explained with the deregulated immune status of the patient. Normally, a T1 response is prevalent in tumor patients, although usually the tumor-specific T cells are ineffective. In our case a shift towards a Th2 immune response is recorded which results in ultimately compromised cell-mediated immunity and might explain the fast development of GBM and the short survival time. Glioma patients generally exhibit a loss of CD4+ cells, a CD4/CD8 ratio close to 1.0 and a mild lymphopenia [5]. Here we report a patient with normal CD4/CD8 ratio but with prominent change in the regulatory T cell lineage. The elevation of the suppressor CD8+CD11b+ cells and the reduction of cytotoxic CD8+CD11b- cells indicate the prevalence of a suppressor phenotype which provides an explanation for the rapid tumor progression and fatal outcome.

CONCLUSION

In conclusion, this case report suggests that the impaired systemic immune response might contribute to the rapid development of multifocal gliomas and play a part in the short survival time.

Acknowledgments:

The study is supported by Medical University, Plovdiv - grant DP-09/2012 and partially by project DUNK -01-2/2009 from the Ministry of Education and Science.

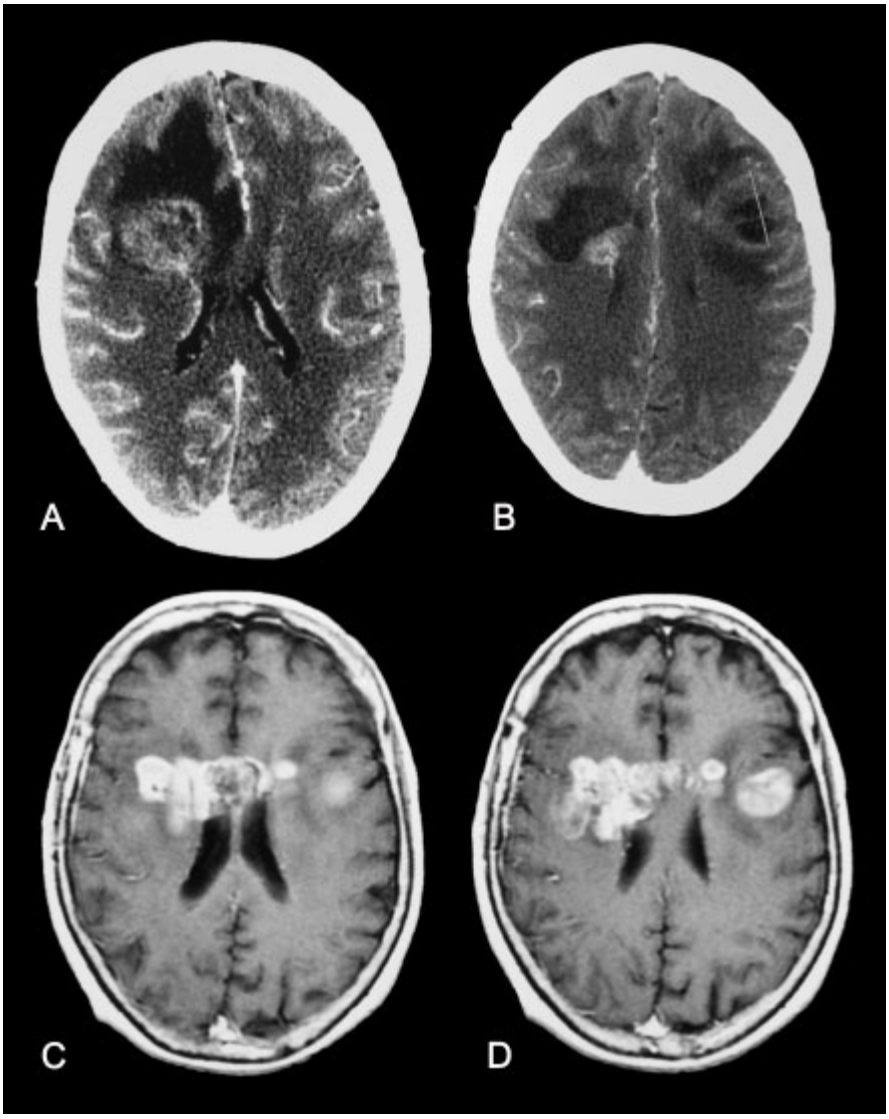

Figure 1.

A. Contrast-enhanced axial brain CT at hospitalization (10 days after the onset of symptoms). Tumor lesion with nonhomogenous structure in the right frontoparietal region.

B. Postoperative (one month after the first surgery) contrast-enhanced axial brain CT. Postoperative alterations in the right frontoparietal region. Appearance of a new heterogeneous tumor lesion in the left frontoparietal region.

C. D. MRI brain images. Axial contrast-enhanced T1-weighted images before the second surgery (1 month and 10 days after the onset of symptoms). Hyperintense lesions with symmetrical localization in both hemispheres expanding to corpus callosum.

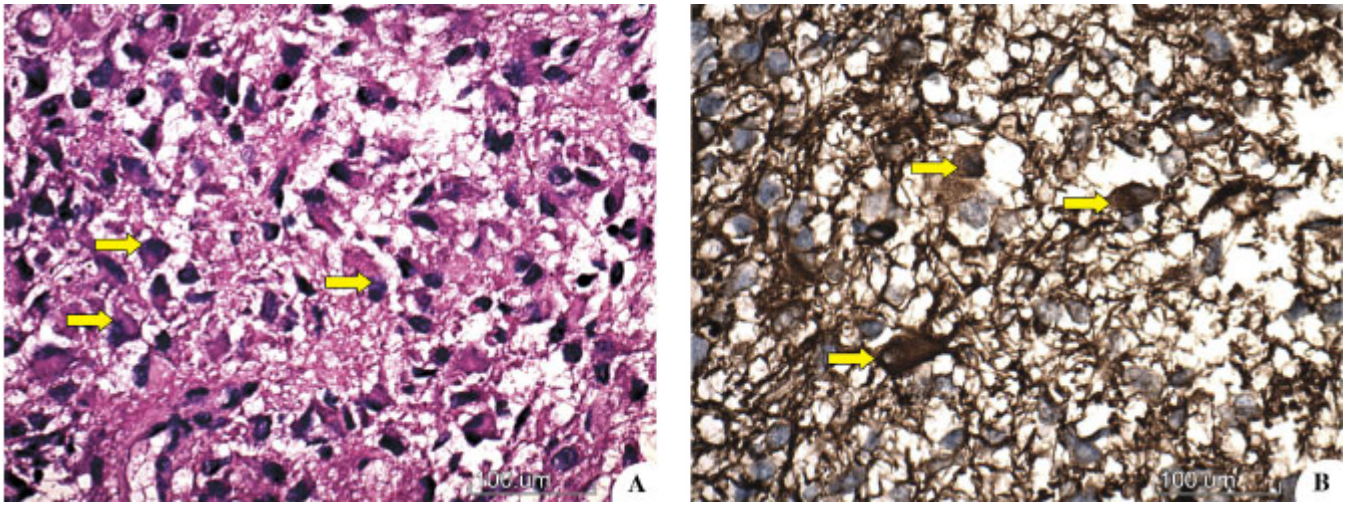

Figure 2.

A. Gemistocytic astrocytes (arrows) within tumor parenchyma. Large cells with abundant eosinophilic cytoplasm rich in gliofibrils and peripherally pushed hyperchromic nuclei. Hematoxylin-eosin staining. Original magnification x 400;

B. Immunohistochemical expression of GFAP (arrows) in neoplastic gemistocytes. Biotin-streptavidin peroxidase method. Original magnification x 400.

REFERENCES:

1. Waziri A. Glioblastoma-derived mechanisms of systemic immunosuppression. *Neurosurg Clin N Am*. 2010 Jan;21(1):31-42. [PubMed] [CrossRef]

2. Kempuraj D, Devi RS, Madhappan B, Conti P, Nazer MY, Christodoulou S, et al. T lymphocyte subsets and immunoglobulins in intracranial tumor patients before and after treatment, and based on histological type of tumors. *Int J Immunopathol Pharmacol.* 2004 Jan-Apr;17(1):57-64. [PubMed]

3. Tihan T, Vohra P, Berger MS, Keles GE. Definition and diagnostic implications of gemistocytic astrocytomas: a pathological perspective. *J Neurooncol.* 2006 Jan;76(2):175-183. [PubMed] [CrossRef]

4. Kaku S, Terao T, Taya K, Ohtuka T, Tanaka T, Sawauchi S, et al. [A multicentric glioma presenting different pathological appearances: a case report.] [Article in Japanese] *No Shinkei Geka*. 2004 May;32(5):501-506. [PubMed]

5. Dix AR, Brooks WH, Roszman TL, Morford LA. Immune defects observed in patients with primary malignant brain tumors. *J Neuroimmunol.* 1999 Dec;100(1-2):216-232. [PubMed]

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