Original article

Viral Infection in Glioblastoma: Immunohistochemistry in Detection of Cytomegalovirus, Epstein-Barr and Herpes Simplex – 1 Virus

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Abstract

Introduction: Glioblastoma (GB) is the most aggressive glial tumor of the brain with a dismal prognosis. Studies conducted during the last two decades highlighted neurotropic viruses as a risk factors involved in development of glioblastoma. Authors present an immunohistological study conducted in a single center on sixty-three archive paraffin-embedded samples of GB.

Patients and methods: The tissues were tested using immunohistochemistry in a homogenous group of sixty-three glioblastoma paraffin-embedded tissues for the presence of Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus type 1 (HSV-1).

Results: Three species of herpes viruses were tested: HSV-1, Epstein-Barr virus (EBV) and Cytomegalovirus using the standard automatized immunohistochemistry. According to the IRS score, there were six samples of HSV-1 regarded as IRS 2 and five IRS 1 samples of the same virus. EBV and CMV were negative.

Conclusion: The result of our study identified HSV-1 as the most prominent neurotropic virus among population surgically treated of GB. Further studies are necessary to confirm its possible oncomodulatory role.

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Introduction

Glioblastoma (GB) is an aggressive primary tumor of the central nervous system (CNS) with median overall survival of fifteen months and the relative five years survival rate of 5%. Current treatment options may be considered ineffective due to aggressive course of glioblastoma. The most common anatomical predilection sites for glioblastoma development are the frontal lobe (25%), the temporal lobe (20%) and the parietal lobe (13%). The occipital lobe (3%) is the rarest supratentorial site and other predilection sites for GB development are medulla oblongata, cerebellum, and the spinal cord (1-3).

The fifth, revised WHO classification of CNS tumors published in 2021 classified gliomas, glioneural tumors and neuronal tumors into six subfamilies. Certain changes have been proposed in division of diffuse gliomas into adult and pediatric type according to its clinical and molecular distinctions. Simplification of the classification of diffuse gliomas in adults includes only three types of tumors: astrocytoma, isocitrate dehydrogenase (IDH) - mutant; oligodendroglioma, IDH mutant and 1p/19q deleted and glioblastoma IDH wildtype (4).

The mechanisms of development of glioblastoma are not yet clearly understood and viral infection presents a possible risk factor in tumor development. It is known that several first tier neurotropic viruses may reach CNS such as John Cunningham virus (JCV), BK virus and simian virus 40 (SV40). The second tier viruses include Herpes simplex virus type 2 (HSV-2), West Nile virus (WNV), Ebola, rabies virus and cause a wider spectrum of symptoms, therefore the role of neurotropic viruses (NTV) in the development of GB has been recently exploited. Recent pandemic recognizes SARS-CoV-2 as a neurotropic virus presenting with neuropathological conditions with yet unclear long term effects (5).

During the last two decades the focus of research has been set on the impact of neurotropic viruses, mostly human herpes viruses (HHV) in the development of glioblastoma. HHV viruses share similar structural and genetic characteristics, consisting of long, linear double-stranded DNA containing up to two hundred genes within the icosahedral capsid. Based on their genetic and biological characteristics, herpes viruses are divided into three subgroups: alpha, beta and gamma. The characteristic of neurotropic HHV viruses is latent viral infection, i.e. the presence of the virus in host cells at rest, but with the maintained potential of reactivation and replication. According to the site of viral latency, the sensory ganglia are the characteristic site for the alpha subgroup. Latency of the beta subgroup HHV is maintained in lymphocytes, kidneys, and secretory glands, while gamma HHVs maintain latency in lymphocyte B and T cells (6).

Recently conducted studies recognized cytomegalovirus (CMV) as the most commonly presented viral pathogenic factor, also the presence of Epstein-Barr virus (EBV) in tumor tissue of glioblastoma has been recently investigated. EBV is a DNA virus which is associated with CNS disorders; its presence in B-cells is well established, resulting mostly in B-cell lymphomas.

In contrast to aforementioned viruses, HSV-1 is best known as oncolytic virus due to its neurotropism and genomic modifiability which result in cellular transcription and translation damage. Viral infections are significantly more common than all bacterial, fungal and protozoal infections according to annual incidence and are most often manifested by milder symptoms, nevertheless more severe infections include death (7).

The aim of our study was to detect the presence of NTV in archive glioblastoma tumor tissue samples surgically treated in a single center in a time period of five years.

Patients and methods

The study was conducted on archival paraffin blocks of sixty-three surgically treated glioblastoma in adults during a time span of five years, from January 1, 2012 until December 31, 2017 at Osijek University Hospital Centre, Osijek, Croatia. The study was approved by the institutional Ethics Committee.

Immunohistochemistry was performed using Ultraview DAB detection kit on automated immunohistochemical Ventana BenchMARK Ultra (Roche®) staining system.

The formalin fixed, paraffin embedded tissue blocks were sectioned at a thickness of 4 μm and then were deparaffinized and rehydrated in graded alcohol and then incubated with HRP multimer. The procedure was continued by hematoxylin counterstaining at room temperature and impregnation in ULTRA LCS (Ultra liquid Coverslip) oil solution.

The staining signal was visualized with 3,3'-diaminobenzidine (DAB) chromogen (Ultra View DAB Copper).

The presence of neurotropic viruses (Epstein-Barr virus (EBV), cytomegalovirus (CMV) and herpes simplex virus (HSV)) were analyzed immunohistochemically with the following antibodies:

- CMV mouse monoclonal antibody (8B1.2, 1G5.2, 2D4.2) - Roche® (Basel, Switzerland) Ready-to-use, part number 06597190001
- Herpes Simplex Virus (10A3) rabbit polyclonal antibody - Dako® (Glostrup, DK-2600, Denmark) Ready-to-use, Type I, part number IR 521, 20068570
- Epstein-Barr Virus, mouse monoclonal antibody, Clones CS. 1-4 - Dako® (Glostrup, DK-2600, Denmark), Ready-to-use, part number 20019280. At each slide we used positive control (infected tissue) and negativne control (buffer, no primary antibody).

All the immunostained slides were scanned and analyzed using the Olympus® CX40 microscope. A positive finding is considered to be staining of the cytoplasm and nucleus in CMV, the cytoplasm and membrane in EBV, and a positive staining of the nucleus in HSV. The interpretation of staining is always associated with the evaluation of positive controls.

The results of immunohistochemical reactions were assessed by the IRS method (immunoreactive score of Remmele and Stegner) according to the percentage of tumor cells in the high-magnification (40x) microscopic field of view. Staining intensity was graded as 0 (negative), 1 (weak), 2 (moderate), and 3 (strong); percentage of positive cells examined was scored as 0 (negative), 1 (≤ 10%), 2 (11-50%), 3 (51-80%), and 4 (≥81%). The two scores were multiplied and the IRS (values from 0-12) was determined. According to this, cases were categorized into four groups: 0-1 as negative (0), 2-3- as weak positive (1), 4-8 as moderate (2) and 9-12 as strongly positive (8).

Results

Immunohistochemistry was conducted on sixty-three archive glioblastoma tumor samples.

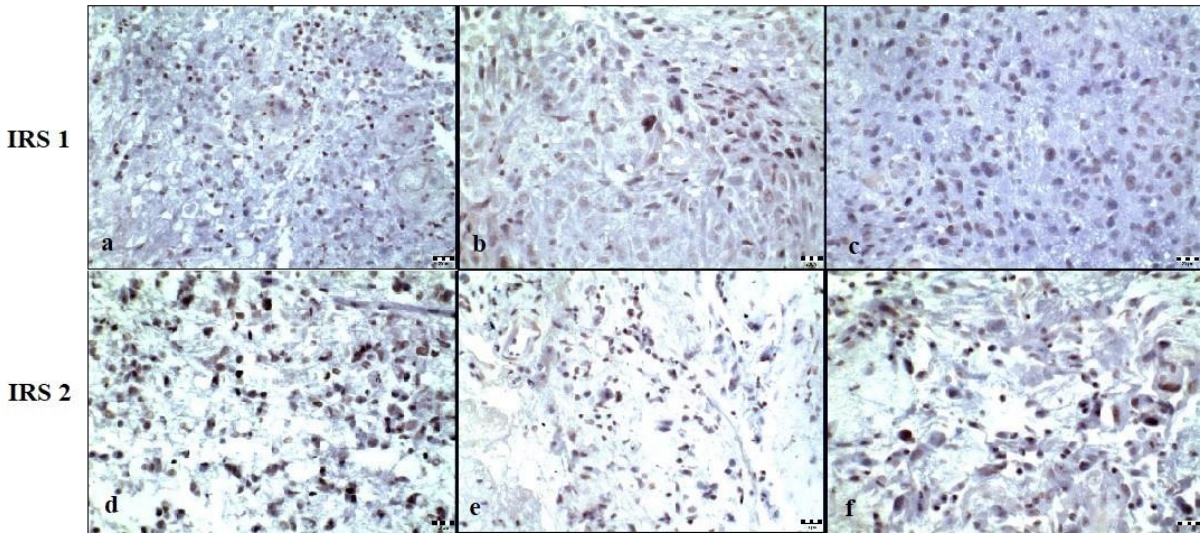

Figure 1. Representative slides of immunohistochemical staining of formalin-fixed paraffin-embedded glioblastoma tissues on HSV-1 antigen graded as IRS 1 (a – c) and IRS 2 (d – f), magnification 400 x.

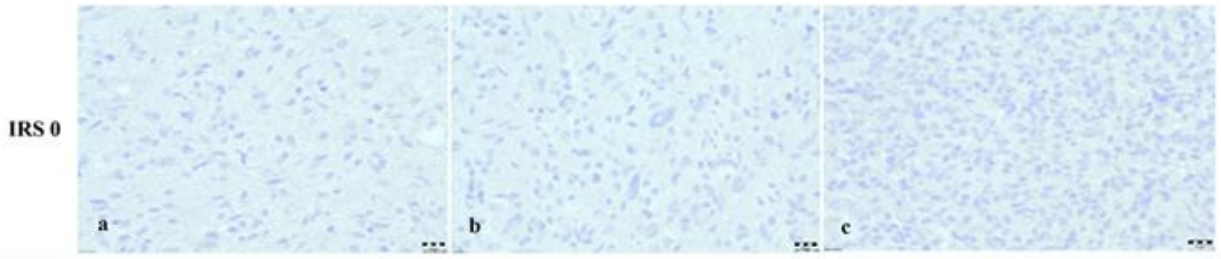

Figure 2. Representative slides of immunohistochemical staining of formalin-fixed paraffin-embedded glioblastoma tissues on CMV (a), EBV (b) and HSV-1 antigen (c) graded as IRS 0, magnification 400 x.

Use of polyclonal antibody HSV 10A3 determined the number of positively stained HSV - 1 nuclei per square millimeter of tumor tissue. The standard automatized immunohistochemistry revealed 5 mildly positive samples which were evaluated as IRS 1 and 6 moderately positive samples evaluated as IRS 2 according to the same semiquantitative assessment (Figure 1.). Use of monoclonal ready-to-use murine EBV antibodies (Clones CS. 1-4) and CMV antibodies (8B1.2, 1G5.2, 2D4.2) excluded the presence of these viruses from paraffin-embedded glioblastoma tissue. The semiquantitative value for CMV and EBV samples was therefore rated as IRS 0 (Figure 2.); additional microscopic evaluation did not reveal the expected staining of the cytoplasm and nucleus in CMV and the cytoplasm and membrane in EBV.

The total percentage of positively stained samples was 17.5%. Semiquantitative results supported the dominant presence of HSV – 1 based on IRS scoring..

Discussion

Glioblastoma still remains an unsolvable problem with an average survival of only 15 months despite numerous technological possibilities and the development of various treatment methods (9). Therefore, current treatment of these tumors can be considered as palliative one with an aim of maintaining the best possible quality of life in these patients. The vast majority of patients are diagnosed with glial tumors in its advanced stage due to the rapid growth of glial tumors and its sudden and progressive symptoms, expressed as headache, focal neurological deficit and epileptic seizures (10).

Extensive studies of the role of neurotropic viruses in glioblastoma have been conducted more intensively over the past two decades with the aim to establish a firm connection between the presence of neurotropic viruses and oncogenesis of glial tumors. The results of all studies are incoherent and do not show a clear insight into the role of neurotropic viruses in oncogenesis and development of glioblastoma.

Research on the role of CMV in glioma tumors began in 2002 with a study conducted by Cobbs et al. The presence of cytomegalovirus gene material in all tested samples was detected by immunohistochemistry and in situ hybridization methods (11). Further research by Scheurer et al. in 2008 and Slinger et al. in 2010 obtained similar results with more than 90% positive samples for cytomegalovirus presence by the same research methods, albeit with a relatively small samples (12,13). Over the next two decades, the results of CMV detection in tumor tissue samples revealed significant discrepancies both in the number and homogeneity of the tested samples and in the research results. Another significant study was enrolled by Libard and co-workers in 2014. They achieved a result of 90% positive samples of glioma tumors for the presence of CMV exclusively by immunohistochemistry. It should be emphasized that out of 469 samples, 219 of them were of glioma origin of all grades. Although various methods of detecting CMV have been used in dozens of studies, no firm consensus has been reached on the role of CMV in the development of glial tumors. Other studies have not

demonstrated the presence of CMV protein or gene material in glial tumor samples despite the use of highly sensitive detection methods, thus also questioning the oncomodulatory potential of cytomegalovirus (14-16). According to the opposite results among studies further need to optimize detection techniques and CMV diagnostics was discussed.

Recent studies were mostly focused on CMV, but novel studies were conducted to elucidate the possible role of EBV in gliomagenesis. EBV is widely spread among the child population and young adults with the possibility of lifelong persistence. Its role is primarily known in pathogenesis of Burkitt's lymphoma and epithelial cell cancers, although presence of EBV in CNS is presented in symptoms such as cerebellar ataxia and disseminated encephalomyelitis or CNS lymphoma which is commonly seen in both immunodeficient and immunocompetent patients. During the last decade a dozen studies were conducted on the role and presence of EBV in glial tumors. Reportedly, EBV DNA is mostly found in high-grade gliomas (type III and IV) in researches that include PCR, IHC and sera testings, although researches based on NGS doubted the connection between EBV and high grade gliomas (17, 18). Less than 5% of primary EBV infections lead to CNS diseases that are clinically manifested by meningitis, encephalitis, cerebelitis, cranial and peripheral neuropathies, as well as polyradiculomyelitis. Mononuclear inflammatory infiltration is characterized by leptomeningeal spread of inflammation with the development of perivascular demyelination. The most common CNS predilection sites for EBV infections are the cerebellum, basal ganglia and less commonly both cerebral hemispheres. Therefore, the most common symptoms are predominantly caused by infection of the thalamic region of the brain, while the highest mortality rate of patients with EBV infection relate to the brainstem (19, 20).

Our study excluded the presence of CMV and EBV, but confirmed the presence of HSV-1 which is the best known as an oncolytic virus (oHSV) with reduced neurotoxicity and retained neurovirulence (21).

A study similar to ours was conducted by Zavala-Vega et al. where authors included CMV, EBV and HSV. They have employed more methods of detection, although their sample group was smaller compared to ours. There was only one case of single HSV infection detected by IHC but at least 50% of HSV infections in their study were mixed infections (HSV and CMV or HSV and EBV) within the group. Overall, more than 70% of their samples were positive for single or mixed infection which was expected given the high seroprevalence of HHV infections among the Mexican population. A clear advantage of their study was a wider array of methods used to increase detection (22).

A possible infection of CNS caused by HSV-1 in adults is presented as herpes simplex encephalitis (HSE); the devastating nature is characterized by brain hemorrhage, brain edema and necrosis mostly affecting the frontal and temporal lobes and the lymbic system. HSV-1 may enter the CNS affecting peripheral neurons or the bloodstream, i.e through the blood-brain barrier (BBB).

Most commonly accepted mechanism of HSV-1 infection of the CNS is its retrograde transport and latent infection of trigeminal ganglia (TG) after peripheral epithelial cells infection. This route of infection is considerably alleviated compared to HSV-1 infection via the bloodstream due to protective cellular barriers between BBB and blood-cerebro-spinal fluid barriers. Besides TG, HSV-1 may also invade other parts of CNS, such as olfactory bulb and orbitofrontal lobe, brainstem, medial temporal lobes and cortex, the limbic system, but it is not correlated to infection of the higher brain areas and projection pathways. Primary infections include mucocutaneous tissue as the "gateway" of infection with consequent distribution of the viral particle. Primary infections occur in the second or third decade of life, with the possibility of reactivation regardless of further age. After primary infection the spread of the viral particle through the neural tissue takes place through the ends of the axon, after which it is

permanently located in the dorsal root ganglion (DRG) (23). Experimental evidence in animal models supports viral transmission via the olfactory or trigeminal nerve, suggesting the possibility of viral spread through the anterior commissure thus achieving viral dissemination of the contralateral temporal lobe (24). Moreover, unlike other cranial nerves with sensory function, olfactory nerve pathways do not pass through the thalamus but are projected directly toward the frontal and temporal lobes (25). Meningeal route of viral dissemination should be taken into account as the consequence of trigeminal innervation of meninges, therefore this route of viral dissemination in HSV-1 infection is not excluded. In addition to direct routes of spreading, reactivation of latent HSV infection of the trigeminal ganglion is another type of pathogenic mechanism of viral activation (26 - 28).

Intermittent reactivation of HSV-1 is mostly caused by immunosuppression, injury of tissues or fever which are conditions frequently found in patients with GB. According to Larjavaara et al., GB is mostly found in the frontal (40%) and the temporal lobe (30%), respectively, which correlates to aforementioned pathways of spreading of HSV-1 through the CNS (29). Therefore, taking into account the anatomical spreading and reactivation of HSV-1 in patients with GB, our results might be explained by the possibility of a high seroprevalence in our population and viral reactivation.

Results of our study can be only partially compared with the results of previously conducted studies in terms of the type of NTV, methods, techniques and the number of patients.

Dominating presence of HSV-1 in our study indicates a possible geographical predisposition and seropositivity among our population and its ethnic groups. The presence of HSV-1 in its latent state in patients with GB and its consequent reactivation is considered to be a result of immunodeficiency in malignant development of GB, although this claim cannot be firmly connected as a role of NTV in development or progression of GB.

Comparing our study to recently enrolled studies, its major limitations were retrospective formalin-fixed paraffin-embedded (FFPE) samples, impossibility of serological testing and limitations in methodology. Even though the total number of samples used in our study was larger comparing to other aforementioned studies, also we used a homogeneous group of histologically confirmed GB. Results from previous studies revealed certain inconsistencies according to different preparation and processing of fresh frozen tissue samples or retrospective samples. Also, genetic variability of population, geographical and racial differences, tumor sample heterogenity and methodologies might explain the different results among studies. Our study was enrolled during the Covid-19 pandemic and furthermore the other possibilities of detecting viruses, such as molecular testing were not included due to the lack of human and technical resources.

Assuming a fact of possible presence of HSV-1 in our population, we have to emphasize that further studies have to be designed to confirm a possible viral influence in the role of development of brain tumors. This claim is confirmed by recent analyses of NTV detection which revealed certain discrepancies related to technical issues and denoted the importance of optimization of staining protocols to obtain unbiased results (30 - 34).

In conclusion, many studies in the last two decades revealed excellent results in their endeavors to clarify the role of NTV in GB, although these results have opened many other inquiries. The importance of further studies is necessary to elucidate the viral oncomodulatory role.

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Competing interests. None to declare.

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Conception and design: NK, IT, ASK
Critical revision of the article for important intellectual content: TP, IT
Drafting of the article: NK
Final approval of the article: TP, IT
Guarantor of the study: JR
Obtaining funding: ASK
Provision of study materials or patients: NK, IT, JR
Statistical expertise: TP, AR

Virusna infekcija i glioblastom: Imunohistokemijsko otkrivanje citomegalovirusa, Epstein-Barrovog virusa i herpes simpleks virusa tipa 1

Sažetak

Uvod: Glioblastom (GB) najagresivniji je glijalni tumor mozga s lošom prognozom. Studije provedene tijekom posljednja dva desetljeća istaknule su neurotropne viruse kao čimbenike rizika uključene u razvoj glioblastoma. Autori predstavljaju imunohistološku studiju provedenu u jednom centru na šezdeset i tri arhivska parafinska uzorka GB-a.

Pacijenti i metode: Tkiva su ispitana metodom imunohistokemije u homognoj skupini od šezdeset i tri parafinski ugrađena uzorka glioblastoma na prisutnost citomegalovirusa (CMV), Epstein-Barrovog virusa (EBV) i herpes simpleks virusa tipa 1 (HSV-1).

Rezultati: Testirane su tri vrste herpes virusa: HSV-1, Epstein-Barrov virus (EBV) i citomegalovirus (CMV) primjenom standardizirane automatizirane imunohistokemije. Prema IRS skoru, šest uzoraka HSV-1 ocijenjeno je kao IRS 2, dok je pet uzoraka istog virusa imalo IRS 1. EBV i CMV nisu bili prisutni.

Zaključak: Rezultati naše studije identificirali su HSV-1 kao najistaknutiji neurotropni virus među populacijom kirurški liječenom od GB-a. Potrebna su daljnja istraživanja kako bi se potvrdila njegova moguća onkomodulatorna uloga.