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Review Article

GLIOBLASTOMA MULTIFORME: A REVIEW OF ITS PATHOGENESIS AND TREATMENT

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ABSTRACT

Glioblastoma multiforme (WHO grade IV astrocytoma) are tumours that arise from astrocytes: the star-shaped cells that make up the "glue-like or supportive tissue of the brain. It is the most malignant types of brain tumour in adults, representing a highly heterogeneous group of neoplasms which are among the most aggressive and challenging cancers to treat. The term GBM was first introduced by Harvey Cushing in 1926 based on the indication that the tumour originates from primitive precursors of glial cells and the highly variable appearance because of the presence of necrosis, hemorrhage and cysts. Despite various modern therapies against GBM, it is still a deadly disease with extremely poor prognosis and has a median survival of 7–15 months from the time of diagnosis. Over 90% of diagnosed glioblastoma multiforme cases are primary gliomas (de novo), which arise from normal glial cells through multistep oncogenesis. The remaining 10% are secondary gliomas develop through the progression from lower grade tumours. Hallmarks of this aggressive cancer include extensive infiltration and strong vascular proliferation into the surrounding brain parenchyma. New approaches to study glioblastoma multiforme and to design optimized therapies are greatly required to address the overwhelmingly poor treatment results for patients currently diagnosed with glioblastoma. This review focuses on GBM epidemiology, etiology, pathogenesis, clinical findings and treatment. In addition, we will highlight recent developments in GBM drug discovery and delivery.

Key words: Glioblastoma Multiforme, WHO grade, genetic alteration, treatment.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and deadliest of malignant primary central nervous system tumour, with a median survival of 7–15 months from the time of diagnosis [1, 2]. These tumours are aggressive and infiltrate surrounding brain tissue. It is classified as a Grade IV (most serious) astrocytoma. The cells in glioblastoma resemble astrocytes cells that normally nourish and support neurons as well as respond to the injury of brain tissue. It is thought that a stem cell or immature astrocyte is the cell of origin that acquires a genetic abnormality and ultimately grows into an entire population of cancerous glioblastoma cells[3, 4]. It develops first and foremost in the cerebral hemispheres but can also grow in other parts of the brain, brainstem, or spinal cord.

Despite various modern therapies against GBM, it is still the deadliest disease with poor prognosis. Patients usually have a median survival of approximately 7 to 15 months from the time of surgical diagnosis [5, 6]. GBM is diagnosed at any age; however the peak incidence is between 55 and 74years. The incidence of GBM in a male to female ratio is about 1.6 to 1.Risk factors for the development of GBM include previous exposure to ionizing radiation and genetic predisposition (such as neurofibromatosis types I and II, li fraumeni syndrome, tuberous sclerosis and turcot syndrome).Working in synthetic rubber manufacturing, petroleum refining, production work, and constant environmental exposure to chemicals, polyvinyl chloride, pesticides have been associated with development of GBM[7].GBM like other brain tumours, produces symptoms which vary depending on the tumour's size, location, and rate of growth. Symptoms include headaches, vomiting, confusion, weakness, numbness, dizziness, seizures, and loss of balance[8].

WHO Grading and Classification

WHO (World Health Organization) classifies gliomas into grade I to IV on the basis of the level of malignancy that is determined by the histopathological criteria[9, 10, 11].

WHO Grade I: ASTROCYTOMA

It is also called as diffuse astrocytoma, a low-grade tumour having the good prognosis and includes special histologic entities which mainly occur in children as under:

i) Juvenile pilocytic astrocytoma: It occurs in children and young adults in the cerebellum, third ventricle and optic nerve pathway.
Macroscopically: Tumors are often cystic or solid and circumscribed.
Microscopically: Predominantly composed of fusiform pilocytic astrocytes having unusually long, wavy fibrillary processes.

ii) Pleomorphic xanthoastrocytoma: It looks histologically pleomorphic and alarming but has a favorable prognosis.

WHO Grade II: DIFFUSE ASTROCYTOMA

It is also called as fibrillary astrocytoma and is the most common form of glioma occurring in 3rd to 4th decades of life.

Macroscopically: Poorly defined, a grey-white tumour of variable size. The tumour distorts the underlying brain tissue and merges with the surrounding tissue.

Microscopically: Composed of well-differentiated astrocytes separated by a variable amount of fibrillary background of

astrocytic processes. Based on the form of astrocytes, three subtypes are differentiated: fibrillary, protoplastic and gemistocytic astrocytoma.

WHO Grade III: ANAPLASTIC ASTROCYTOMA

It generally evolves from the lower grade of astrocytoma

Macroscopically: Anaplastic transformation may be associated with little macroscopic change from astrocytomas. Even though on MRI, areas undergoing anaplastic progression often show contrast enhancement

Microscopically: Contains features of anaplasia such as hypercellularity, pleomorphism, nuclear hyperchromatism and mitosis. An additional characteristic feature of anaplastic variety of astrocytoma is the proliferation of vascular endothelium. However, necrosis is not present.

WHO Grade IV: GLIOBLASTOMA MULTIFORME

Although its nomenclature means its origin from embryonic cells but now it is known that this tumor arises by neoplastic transformation of mature astrocytes. It is the most aggressive of astrocytomas.

Macroscopically: GBM distorts the normal anatomy of the brain. Foci of cyst formation, necrosis and hemorrhage are mixed with mucoid gray neoplastic tissue. GBM generally appear as spherical masses with a necrotic center that may be seen on MRI as a ring enhancing mass.

Microscopically: Necrosis and a florid microvascular proliferation are the key features separating GBM from the two other astrocytic neoplasms. It has highly anaplastic and cellular appearance. The cell types show marked variation consisting of fusiform cells, small poorly-differentiated round cells, pleomorphic cells and giant cells. Microvascular endothelial proliferation is marked. It shows areas of tumour necrosis around which tumor cells may form pseudopalisading[9, 10, 11].

EPIDEMIOLOGIC FEATURES

GBM is the most aggressive malignant primary brain tumourwith global incidence rate ofless than 10 per 100,000 people, its poor prognosis with the survival rate of 7-15 months after diagnosis makes it a crucial public health issue [12]. Males are more commonly affected by glioblastoma multiforme, with an incidence rate of almost 1.6 times higher than in females.GBM can take place at any age however, the peak incidence is between 55 to 74 years. Anaplastic astrocytomas occur in younger adults between ages 30 -50 and account for 17% of primary malignant brain tumors. Only 9% of brain tumors in children are glioblastomas. 1 to 7% of people with glioblastomas and 4% of people with anaplastic astrocytomas are found to have multiple tumours at the time of diagnosis. The incidence of gliomas is usually higher in the western world compared to less developed countries that could be due to under reporting of gliomas cases, limited access to health care and differences in diagnostic practices[13, 14].

ETIOLOGY OF GBM

The exact underlying etiology of GBM has not been fully elucidated. They are believed to be the result of genetic mutations that result in the uncontrollable growth of specific types of brain cells. Factors that may cause GBM are:

- It can be caused by a genetically inherited syndrome, such as Neurofibromatosis, Li-Frameni, Von HippelLindau, Turcot and Tuberous Sclerosis, but these only affect 5% of patients [15, 16].
- It is rare for glioma to run in families. However, having a family history of glioma can double the risk of developing it. A number of genes have been weakly linked with glioma, but more study is needed to authenticate a link between the genetic variations and brain tumours.
- Viruses, such as human cytomegalovirus (HCMV), are also believed to be among the etiologic agents for glioma development [17].
- Constant exposure to Ionizing radiation, chemicals such as pesticides, polycyclic aromatic compounds and solvents increase the likelihood of developing this type of tumour.
- It is also considered as an occupational disease as the persons working in the rubber and petrochemical industries are believed to be at a higher risk of glioma incidence [18].

PATHOPHYSIOLOGY OF GBM

GBM originate from glial cells, or their precursors, within the central nervous system. However, recent studies suggest that astrocytes, oligodendrocyte progenitor cells and neural stem cells could also serve as the cell of origin. 90% of thistumour occurs in the white matter of the cerebral hemispheres within the corticotemporal region of the brain while only few percent of tumours occur in cerebellum, brainstem and spinal cord. GBM is unique due to the presence of necrosis and vascular proliferation[19].

PRIMARY AND SECONDARY GLIOBLASTOMA MULTIFORME

GBM can be classified into primary and secondary GBM.

Primary GBM
Also termed asde novo glioblastoma; as they arise without any clinicalor histopathological evidence of less malignant precursor lesion. The majority of GBMs (90%) are primary, patients with primary GBMs tend to be older (mean age = 55 years) and developed more frequently in men with median survival rate of 4.7 months.

Secondary GBM
They develop initially from low-grade diffuse astrocytoma or anaplastic astrocytoma with clinical and histopathological evidence**.** Secondary GBMs are rare at the population level, accounting to only 10% of all glioblastomas and manifest in younger patients (mean age = 40 years) and occur more frequently in women with median survival rate of 7.8 months. [20,21].

GENETIC ALTERATION IN PRIMARY AND SECONDARY GLIOBLASTOMA

Genetic alterations for primary GBMs are EGFR over expression, PTEN mutation, and loss of chromosome 10. Genetic alterations seen in secondary GBMs include IDH1 mutations, TP53 mutations, and 19q loss.

Epidermal Growth Factor Receptor (EGFR): It is a cell surface receptor that is involved in the control of cell proliferation and plays an important role in the development of primary glioblastomas. In 40% of primary glioblastomas amplification of the EGFR occurs, which occur rarely in secondary glioblastomas resulting in an inframe deletion of exons 2-7 from the extracellular domain, causing a shortened mutant receptor known as EGFR variant III. This shortened mutant receptor is therefore ligand-independent and constitutively active which confers extreme tumourigenicity on glioma cells by increasing proliferation and reducing apoptosis. Overexpression of EGFR is

seen in 50%-60% of GBMs with the most common EGFR mutation (EGFRvariantIII) expressed in 24%-67% of cases[20].

Phosphatase and Tensin Homology (PTEN) mutations: This gene is positioned at 10q23.3 which encodes a central domain alongside homology to the catalytic region of protein tyrosine phosphatases, as it is important in the function of protein phosphatase and 3-phosphoinositol phosphatase activities. This gene is mutated in 15 to 40% of glioblastomas, predominantly in primary glioblastomas.

Loss of Heterozygosity (LOH): The most common genetic alteration occurring in primary and secondary GBM IS LOH 10qwith a common deletion at 10q25-qter. In contrast, LOH 10p is mostly present in primary glioblastomas, and complete loss of the entire chromosome 10 is characteristic for primary glioblastomas. According to several studies, LOH occur commonly at three deleted loci which are: 10p14-p15, 10q23-24 (PTEN), and 10q25-pter, specifying the presence of several tumour suppressor genes that can play significant roles in the pathogenesis of glioblastomas. As LOH 10q25-qter is associated with histologically known transition from low-grade or anaplastic astrocytoma to glioblastoma phenotypes and it is deleted in both glioblastomas, the tumor suppressor gene(s) present at these loci appear to be involved in the pathogenesis of primary and secondary glioblastoma [20].

TP53 mutations: The protein p53, with a gene positioned at 17p13.1 is one of the main tumour suppressors. It is a transcription factor that activates genes expression which will induce the G1 cell cycle arrest in response to DNA damage and cell stress. Thus, the somatic and the germ line mutations of p53 are associated with a variety of human cancers. This TP53 pathway plays a crucial role in the development of secondary glioblastomas. It also occurs in primary glioblastomas, but at a lower frequency. 57% of mutations have been reported to be located in the two hotspot codons 248 and 273 in secondary GBMs whereas in primary GBMs, mutations were more equally distributed through all exons, with only 17% occurring in codons 248 and 273. Additionally, G:C A:T transitions at CpG sites, considered to result from deamination of 5-meC, were significantly more frequent in secondary than in primary glioblastomas[20].

Isocitrate dehydrogenase (IDH) mutation: The genes IDH1 and IDH2 are molecular markers which demonstrate prognostic value in patients with GBM.Approximately 80% of grade II, grade III gliomas and secondary GBMs harbor a single amino acid missense mutation in gene IDH1 at arginine 132.The IDH2 mutation at arginine 172 is less common and is exclusive with mutations in IDH1. IDH1 and IDH 2 mutations promote a neomorphic reaction in which the normal product α-ketoglutarate is converted to 2-hydroxyglutarate (2-HG) (oncometabolite) in a reaction. D-2 HG controls the oncogenicity of IDH mutations. Based upon mutation status, gliomas may be categorized as IDH-wild-type or IDH-mutant. IDH-wild-type gliomas include gradeI and primary GBM. IDH-mutant gliomas include grade II, grade III gliomas and some secondary GBM. The collection of high concentrations of 2- HG has been shown to contribute to the formation and malignant progression of gliomas[22].

MOLECULAR DIAGNOSTIC SIGNATURE OF GLIOBLASTOMA

The classification of Glioblastoma multiforme based on gene expression distinguishes into four subtypes which are: Classical, Proneural, Mesenchymal and Neural.

Classical: The classical subtype features of GBM are

- Amplification of chromosome 7 and chromosome 10 deletion.
- Mutation/amplification/ over expressionin EGFR (epidermal growth factor receptor).
- Abnormalities in genes such as TP53, NF1, PDGFRA, or IDH1 are not found in this group.
- Respond significantly better to aggressive treatment, patients in this group lived the longest compared to those in the other groups[23, 24].

Proneural: The Proneural subtype features of GBM are

- Amplification of chromosome 7 and chromosome 10 deletion are less prevalent.
- High rates of modification in TP53 (p53), and in PDGFRA, the gene encoding a-type platelet-derived growth factor receptor, andpoint mutations in IDH1, the gene encoding isocitrate dehydrogenase-1.
- Shows high expression of oligodendrocytic development genes (e.g., PDGFRA, NKX2-2 and OLIG2) that may help explain its atypical GBM subtype status.
- No difference in response to aggressive treatment and often associated with secondary GBMs[25, 23].

Mesenchymal: The mesenchymal subtype features of GBM are

- High rates of alterations in NF1, the gene encoding Neurofibromin1.
- Mutation in the PTEN and TP53 tumor suppressor genes.
- Inflammation and higher fraction of necrosis in this sub group.
- Respond better to aggressive treatment, patients survive longer than those in the proneural and neural groups[25, 23].

Neural: The neural subtype features of GBM are

- Expression of neuron markers such as NEFL, GABRA1, STY1, and SLC12A5.
- Associated with neural, astrocytic and oligodendroctyic gene signatures
- Some improvement in survival of patients but not as significant as in the classical and mesenchymal groups of patients [25, 23].

CLINICAL SIGNS OF GBM

Symptoms of GBM, vary with each individual depending on the size and location of the tumor and usually present late in the course of the disease, and the most common clinical signs are those of increased pressure within the brain, which include headaches, dizziness, ataxia, vision disturbances (blurred vision, diplopia), and recurrent syncope. In addition, one third of patients experience at least one epileptic seizure.GBM grow rapidly and may infiltrate nearby normal brain tissue, ultimately leads to life-threatening complications[26, 8].

DIAGNOSIS

The diagnosis of GBM is based on a clinical evaluation, a detailed patient history, neurological examination and a variety of imaging techniques including CT scan and MRI

- CT (Computed Tomography) brain scan is a specialized X-ray. During scanning, a computer and x-rays are used to create a film showing cross-sectional images of certain tissue structures. This will take 20-30 minutes. This scan will help to determine the size, location and probable type of tumor.
- MRI (Magnetic Resonance Imaging) brain scan is a specialized imaging technique which gives clear pictures of the brain and will show the location and extent of atumour. It usually takes 30 to 40 minutes and uses the magnetic field and radio waves instead of x-rays. It is considered as the primary diagnostic tool for GBM. With contrast, high-grade gliomas

show enhancement; low-grade gliomas normally do not enhance with contrast or slightly enhance on MRI. The examination of a patient's tumour tissue under a microscope and molecular analysis can only confirm an exact diagnosis of GBM[27].

- MRS (Magnetic Resonance Spectroscopy) is a noninvasive diagnostic examwhich measures chemical and mineral levels present in a tumour. These measurements give anidea as to whether a tumour is malignant or benign. It also help to differentiate a brain tumour from other medical problems, such as infection (bacterial, parasitic and fungal), demyelination or a stroke[28].
- Positron emission tomography (PET) which is a nuclear medicine technique, being employed as problem solving tools to differentiate between an active tumour and therapy-related changes in tumour[29].
- A surgical removal or biopsy may be performed by a neurosurgeon who extracts a small sample of abnormal cells to test in a pathology laboratory and the microscopic evaluation may confirm a diagnosis. The main clue to a tumour's being glioblastoma multiforme is the cell necrosis or cell death that is characteristic of GBM[30].

GLIOBLASTOMA MULTIFORME THERAPY

The standard treatment for GBM includes surgical resection, radiotherapy and chemotherapy.

Surgery

Complete surgical resection, represent the most effective way to increase survival of GBM patients, is hardly promisingas it depends on tumor size, shape, localization and infiltration, especially when highly specialized brain areas are involved such as those areas which control speech, motor function, and the senses. The penetrative behavior of GBM makes surgery ineffective, as tumour cells and glioblastoma stem cells (GSC) colonize the surrounding brain areas which may leads to later disease recurrence or progression[31].

The advances in surgical treatment make use of 5-aminolevulinic acid (5- ALA) dye for fluorescence guidance has been found to be more effective to assist neurosurgeons to differentiate between normal brain cell and residual tumor cell tissue. The ALA induces the acquisition of porphyrins particular to glioblastoma which show fluoresce under violet-blue light. The color difference between the porphyrin-containing tumour and adjacent normal brain tissue allows for more specific and thorough resection of tumour cells. 65% of resections by ALA attained complete resection, while only 36% met complete resection criteria by using conventional methods. Other fluorescent compounds such as sodium fluorescein, are being tested to provide better resolution for optimal resection [32].

Radiation Therapy

After optimal surgical resection, the patient waits 4 weeks for the craniotomy wound to heal and then starts radiotherapy to kill the remaining tumour cells. It improves life expectancy for all patients with grade III and IV gliomas[33]. Conventional fractionated external beam RT (EBRT), 6 weeks of localized radiation therapy given 5 times per week is the standard radiation therapy for GBM. Major hurdleswith radiation therapy are the invasive nature of GBM, radiation necrosis, radiation-induced permanent neuronal damageand radiation resistance of some tumours[12]. Despite serious risks, a number of more focused techniques, such as brachytherapy, hyperfractionation, and the combination of EBRT with stereotactic radiation have been investigated, however none shown to be superior to standard EBRT[8].

Chemotherapy

The standard chemotherapy for GBM patients is TMZor temozolomide. It was first described in 2005, is a brain-penetrant alkylating agent which methylates purines (A or G) in DNA and trigger apoptosis. When TMZ was given concurrentlywith radiotherapy it increases median survival rates to 26.5% at 24 months, in newly diagnosed GBM.

The mechanism responsible for the cytotoxicity of TMZ is to methylate DNA at the N3, N7 and O6 position on adenine and guanine residues respectively which leads to the failure of DNA mismatch repair system in order to locate a complementary base for methylated guanine thereby resulting in DNA damage and subsequently inhibits the cell cycle at the G2-M phase and triggers apoptosis [33]. The methylated adenine, guanine bases can be repaired mainly by DNA repair enzyme systems that reverse guanine methylation induced by tomozolomide, thus avoiding apoptosis initiation. The resistance to temozolomidedepends on different DNA repair systems, among which methyl guaninemethyltransferase (MGMT) shows great interest. High levels ofMGMT activity in tumour cells are mainly responsible for poor TMZ response. MGMT is a mediator of DNA repair protein that protects tumour cells against alkylating chemotherapeutic agents. However, TMZ has slightly improved the survival of GBM patients, it is also likely for inducing many side effects[32]. To overcome the resistance mechanism, capecitabine and TMZ combination was designed. Capecitabine is a prodrug of the pyrimidine analog 5-fluorouracil that is converted to 5-FU and leads to inhibition of MGMT repair activity, possibly through depletion of MGMT protein and mRNA [34].

The other alkylating agents like carmustine or BCNU (bis-chloroethylnitrosourea), lomustine (CCNU) Gliadel wafer and Vicristine are severely cytotoxic drugs which are design to destroy tumour cell and treatment with these drugs results in early development of resistance that further limits their benefit and they are also associated with many side effects such as Nausea, myelo suppression, pulmonary fibrosis [32].

NEW STRATEGIES

Nanoparticles

Nanoparticles are particles in the nanometer size range comprise of different structures and properties and are extensively studied for biomedical applications. They offer a potential means tooptimize drugs delivery to brain tumors, by enabling better permeability through the Blood brain barrier and specifically targeting tumour cell Several nanoparticle types are under investigation with different application strategies in the treatment of GBM.

One such is lipid carriers (Liposomes) which are bilayered vesicles composed of phospholipid membranes. Liposomes are highly flexible, can be loaded by a variety of drugs and are extremely biocompatible. The chemotherapeutic drug Paclitaxel is not capable to cross blood brain barrier and for this reason, not useful for brain tumour treatment. In GBM treatment, liposomes are loaded with the paclitaxel drug, in order to make it crossthe blood brain barrier. The other drugssuch as monoclonal antibodies, peptides, siRNA and other molecules, which areotherwise unable to cross the blood brain barrier are under investigation for use in the treatment of GBM as liposome formulations[35].

Oncolytic Viruses

Oncolyticvirotherapy (OV) has potential use in the treatment of GBMas they precisely target cancer cells. They have been

designed to take advantageof tumor-specific mutations, or signaling pathways which are constitutively activated in tumours, and are chosen to enter over expressing tumour cells. The infected tumour cells thereby undergo apoptotic processes or necrosis and eventually leads to cell death.

Severaloncolytic viruses are under investigation for GBM treatment, including Herpes simplex virus 1 (HSV1) and adenovirus (AdV). HSV1, an enveloped DNA virus, which contains double-stranded DNA. A number of HSV mutants such as HSV-1716, R3616, hrR3, G207, and G47D have been designed for targeting glioblastoma and these mutants show deleted or mutated viral genes, hence reducing neurotoxicity.

Adenovirus is medium sized, non-enveloped virus containing a double-stranded, linear DNA genome. AdV trials have begun by using DNX-2401 and ADV-TK.DNX-2401 alteration allow for replication only in the cells which bear Retinoblastoma protein tumor suppressor deletion. The addition of a cyclic arginine/glycine/aspartic acid (RGD-4C) peptide gives the virus high affinity towards RGD-binding integrins, increases oncolytic activity against GBM.

ADV-TK is an adenoviral vector designed to express the Herpes thymidine kinase gene. When use in combination with anti-herpetic prodrug ganciclovir (GCV) may provide promising approach in the treatment of malignant glioma. ADV-TK gene therapy demonstrated a progression-free survival and found to be safe, by a randomized phase II clinical trial[35, 32].

Immunotherapies

Immunotherapy for GBM has gained a considerable interest in research field as it offers different approaches from other GBM therapies, raising new hopes particularly for immune checkpoints inhibitors which mainly include therapeutic targeting of immune checkpoint programmed cell death (PD)-1 receptor and programmed death ligand (PD-L1), that destroy the activity of T lymphocytes by inducing programmed cell death in activated immune cells. The PD-L1expression is seen in glioma cell lines and tumour tissues. It was also reported that expression of PD-L1 was greater at the edges of the tumours rather than in the tumour cores, thereby leading to the formation of an obstacle between the tumour and cytotoxic T cells whichis defined as “molecular shield”. The approach of inhibiting PD-1 and PD-L1 by Monoclonal antibody has given significant results in the treatment of several human malignancies. The other new immune-cells based approaches are genetically engineered chimeric antigen receptor (CAR T)/NK cells. These are designed to recognize GBM antigens such as IL13Rα2, EphA2, HER2 and EGFRvIII and are currently undergoing several phases I/II trials in humans[34].

CONCLUSION

Glioblastoma multiforme is the commonest and deadliest malignant brain tumour with poor clinical outcome. It is heterogenic and has very complex pathology and multiple mechanisms of cell proliferation and growth. The traditional treatment for GBMsuch as surgery resection, radiation and chemotherapy, still considered to be the first line approaches to GBM, hopes to improve survival rates and overall life expectancy of GBM patients. Early diagnosis may be a key to improve survival rates of patients through prevention of tumour growth and identification of early biomarkers is necessary.

A variety of new techniques are currently undergoing research, alone or in combination and development of new strategies or chemotherapeutic agents may offer therapeutic advantages in the future. The improved understanding of GBM may allow for more effective therapy selection for patients, thereby can extend survival in the coming years.

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