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The probable progression of Epstein-Barr virus (EBV) to chronic active EBV/reactivation weakens the immune response and stimulates *Cryptococcus neoformans* infection, which invariably proves fatal: a case report and review of the literature

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We have reported here the fatal outcome of Epstein-Barr virus (EBV) infection in a 58-year-old male who had probably developed reactivation/chronic active EBV (CAEBV) which gave rise to various neurological deficits, pancytopenia, and a lower CD4 count in the patient. The decreased immune response helped *Cryptococcus neoformans* (*C. neoformans*) to manifest a disseminated infection. Although he was exclusively provided with antifungal treatment and the patient appeared to be successfully treated for cryptococcal infection, no coverage of EBV appeared detrimental as the patient died the very next day. This report highlights the need for clinical suspicion of EBV in unexplained cases of neurological manifestation, the hematological disorder of pancytopenia, a lower CD4 count, and multiorgan involvement such as pleural effusion, coarse liver echotexture, and splenomegaly.

KEYWORDS

EBV (Epstein-Barr virus), chronic active EBV, reactivation, immunosuppression, disseminated cryptococcosis

1 Introduction

The prevalence of Epstein-Barr virus (EBV) infection is observed to be more than 90% in the adult population worldwide (1). It is mostly asymptomatic in childhood, while nearly half of the infected population tend to develop symptoms by the time they reach adulthood, which is mainly self-limiting. Furthermore, EBV is established as a latent infection awaiting reactivation/chronic active EBV (CAEBV) upon decreased immunity. Reactivation of EBV/CAEBV leads to various clinical manifestations, including meningitis, encephalitis, optic neuritis, autoimmune diseases, and various malignancies (2). These manifestations also hamper CD4 T cell count to weaken cellular immunity. Weakened cellular immunity provides a conducive environment for other pathogens such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and *Cryptococcus* spp., making both diagnosis and treatment management complex and difficult. CAEBV is rare and characterized by a high viral load, increased anti-EBV antibody response, pancytopenia, and T/natural killer (NK) cell lymphoproliferative diseases (1).

Cryptococcus neoformans (*C. neoformans*) causes various infections such as disseminated cryptococcosis and meningitis, which are mainly observed in HIV-positive patients with increased mortality. In HIV-negative patients, the clinical significance of the co-occurrence of EBV with cryptococcal infection has been scarcely reported (3, 4). Herein, we provide a case report of a 58-year-old deceased patient with a coinfection of EBV and *C. neoformans* after receiving the due consent from his wife. The requirement of ethical approval was waived by the Institutional Ethics Committee, AIIMS Raipur, as per their policy of not requiring ethical permission in case reports and only consent from the patients is sufficient with due information to the ethical committee. The studies were conducted in accordance with the local legislation and institutional requirements.

2 Case history

A 58-year-old male presented to the All India Institute of Medical Sciences (AIIMS) Raipur Trauma and Emergency in April 2024 with complaints of bilateral lower limb weakness for 1 year with recent onset of breathlessness, mMRC 2 (Modified Medical Research Council) for 10 months, which progressed to mMRC 4 in the previous 6 weeks, and intermittent low-grade fever associated with chills that were relieved with symptomatic treatment. The bilateral lower limb weakness (right > left) started distally and progressed proximally, followed by bilateral upper limb weakness for 3 months. On clinical history evaluation, the patient was found to be non-diabetic and non-hypertensive but hypothyroid for 2 years and an alcoholic for 20 years. A history of bilateral pneumonia was noted in the last week of January 2024, which improved upon treatment in a private hospital with levofloxacin, amoxy-clav, prednisolone, and hydrocortisone nebulization, and the patient was discharged. However, similar symptoms recurred once again in mid-March and the patient was treated similarly. However, with the progression of his worsening condition, he was referred to our hospital. We followed the CARE case report guidelines for the diagnostic investigations, treatment, and outcome (Supplementary Table 1).

The day-wise hematological, renal, liver, and inflammatory investigations were recorded (Table 1A). On examination, his Pulse Rate (PR) was 61/min, Blood Pressure (BP) 104/74, RR 17/min, and saturation of peripheral oxygen (SpO2) of 99%. Bilateral pitting edema, pallor, and clubbing were present with bilateral inspiratory coarse crepitations. The patient was subsequently shifted to the Medical High Dependency Unit (HDU) and was treated for hospital-acquired pneumonia with vancomycin 1gm q8h iv and meropenem 1 gm 8h iv. The summarized timeline of the patient's clinical condition, treatment, and investigation is provided in Table 1B.

Hence, in view of the pancytopenia, bone marrow aspiration and bone marrow biopsy were conducted, the results of which were found to be insignificant. The patient was started on romiplostim 250mcg once weekly subcutaneously with repeated random donor platelet transfusions. CD4+ T helper cell count was 149. A nerve conduction study revealed pure motor polyradiculoneuropathy with the neurogenic pattern on an electromyogram (EMG). In contrast-enhanced computed tomography (CECT), lung consolidation with bilateral pleural effusion and splenomegaly were noted. Ultrasonography (USG) of the abdomen revealed a coarse echotexture of the liver with a prominent portal vein and splenomegaly.

The patient was non-reactive to HIV (HIV1/2 Immuno chromatography Lateral flow Assay kit, (Pathkits, India, Lot No. PKRK/014/0424-07), Hepatitis B (HBsAg Rapid Immuno chromatography lateral flow assay, Med Source Ozone Bio Pvt. Ltd., Lot No. HBSC210324L), Hepatitis C (HCV Rapid Immunochromatography lateral flow Assay kit, BIOGENIX INC.PVT.LTD, Lucknow India, Lot No. HCV 0324), and Dengue (ErbaQik Dengue DUO NS1 Ag with IgG/IgM Immuno chromatography assay, Erba Manheim, India, Lot No. DRDDO2302B). Multiple blood cultures were collected and incubated in a BacT/Alert automated blood culture system which flagged positive after 48 hours of incubation. Gram staining from the positive blood culture bottle revealed the presence of gram-positive budding yeast cells. The positive blood culture bottles were then subcultured onto blood agar and Sabourauds dextrose agar (SDA) which grew mucoid white creamy pasty round colonies after 48 hours of aerobic incubation at 37°C and was found rapid urease positive. It was also identified as *C.neoformans* in the Vitek2 automated system (bioMerieux Inc, USA with the use of Vitek yeast (YST) card Lot No. 2432243503). The cerebrospinal fluid (CSF) cytology reported slightly elevated leukocytosis (150 cells/ml) with a protein level of 127mg/dl and glucose level of 69mg/dl. A rapid Cryptococcal antigen test of the patient's CSF (Crypto PS Rapid Immunochromatography lateral flow Assay, BIOSYNEX SA, France with Lot No. KCC240226) was found to be positive. CSF India ink microscopy identified capsulated round budding yeast cells while the culture grew *C. neoformans* (Figure 1). The isolate was sensitive to fluconazole, flucytosine, and amphotericin B with minimum inhibitory concentrations (MICs) of 1µg/ml, 2µg/ml, and

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TABLE 1A Day-wise hematological, renal, liver, and inflammatory markers in the patient.

Parameter	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Hematologic						
Hemoglobin (gm/dl)	7.6	6.3	6.7	5.1	6.6	7.6
Total Leukocyte Count (/μL)	2040	2370	4070	2100	3100	1870
Platelet Count (/μL)	45	26	26	30	12	19
Renal Function Test						
Sr. Urea (mg/dl)	22	22	47	62	87	107
Sr. Creatinine (mg/dl)	0.6	0.4	0.7	1.3	1.5	2.15
Sr. Sodium (mEq/L)	130	134	132	131	145	139
Sr. Potassium (mEq/L)	4	2.4	3.5	4.4	2.9	5.6
Liver Function Test						
Total Bilirubin (mg/dl)	0.7	1.1	1.3	1.4	1.8	1.68
AST (U/L)	169	110	101	104	79	64
ALT (U/L)	49	31	22	35	27	17
Inflammatory Markers						
C-Reactive Protein (mg/dl)	28.3	20.3	94.2	99.2	11.7	181.3
Procalcitonin (μg/L)	0.8	-	-	0.33	0.24	3.86

Sr, Serum; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase.

TABLE 1B Timeline detail of the patient's treatment and investigation.

Major Issues	Week 1	Week 2	Week 3	Week 4
Hospital Acquired Pneumonia	Meropenem 1gm q8h* Vancomycin 1gm q8h*	Septic Shock escalated to Tigecycline 200 mg stat f/b 100mg q 12h iv* and Colistin 9MU stat f/b 4.5 MU q 12h iv*	Shock Resolved Hemodynamically Stable	Deterioration ARDS Septic Shock Seizures
Pancytopenia	Persistent Thrombocytopenia and Leukopenia ; No Nutritional Deficiency; ANA - Negative *Worsening Anemia ?Amphotericin-B Induced ? Sepsis-Related* *Peripheral Smear and Bone Marrow* – Normal ; Ferritin > 1650 ng/ml			
Weakness	Nerve Conduction Study – Pure Motor Polyradiculopathy MRI Brain and Spine – Intramedullary T2/FLAIR at D12 Vertebra & Cerebral Atrophy			
Cryptococcus neoformans	Blood and CSF Culture – *Cryptococcus neoformans* ; Liposomal Amphotericin-B 5mg/kg/day (350mg/day) Started on Day 8 Amphotericin Dose reduced to 3mg/kg/day for Suspected Drug Induced Anemia	Flucytosine 25mg/kg q6h #	Culture Negative on Day 10 of Therapy	
Empirical Anti-Tubercular Therapy	Contrast CT – Chest & Abdomen - No evidence of TB Sputum AFB. CB-NAAT: *Mycobacterium tuberculosis*		Day 22 Suspected Spinal Tuberculosis Started on ATT$	
Epstein-Barr Virus				EBV VCA IgG Positive EBV DNA PCR - Detected

#Given for 8 days due to financial constraints; *Given for 7 days; $ATT, Antitubercular drug: Rifampicin 600mg OD, Isoniazid 300 mg OD, Pyrazinamide 1100mg OD; AFB, Acid Fast Bacilli; ANA, Anti=Nuclear Antibodies; ARDS, Acute Respiratory Distress Syndrome; CT, Computed Tomography; CB NAAT, Catridge Based Nucleic Acid Amplification; EBV, Ebstein Barr Virus; f/b, followed by; FLAIR, Fluid Attenuated Inversion Recovery ivIntravenous; MRI, Magnetic Resonance Imaging; OD, Once Daily; PCR, Polymerase Chain Reaction; VCA IgG, Immunoglobulin G against Viral Capsid Antigen.

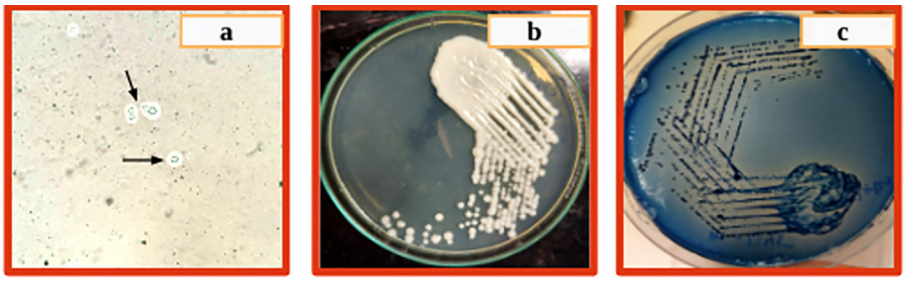

FIGURE 1
(A) Circular yeast cells with capsule and narrow-based budding, **(B)** White creamy pasty mucoid colony on SDA after 48 hrs incubation, **(C)** Blue colonies on Cryptococcal differential media after 48 hrs incubation.

0.5µg/ml respectively tested by the Vitek2 system using Vitek2 antibiotic sensitivity testing (AST)-YS08 card, Lot No. 2882831503. He was started on flucytosine 25mg/kg q6h and liposomal amphotericin B 5mg/kg/day (350 mg) which was reduced to 3 mg/kg/day due to suspected drug-induced thrombocytopenia. Despite laboratory evidence of the clearing of the cryptococcal infection in the blood culture, the patient's condition worsened. He was urgently started on tigecycline and colistin. Magnetic resonance imaging (MRI) of the brain with the spine showed a short segment with ill-defined intramedullary T2/Fluid-Attenuated Inversion Recovery (T2/FLAIR) of 14.3 mm at the Thoracic Vertebral level 12 (T12) region and brain atrophy. With a clinical suspicion of spine tuberculosis, the patient was started on antitubercular (ATT) drugs. However, *M. tuberculosis* was not detected in a cartridge-based nucleic acid amplification test (CBNAAT) on Genexpert (Cepheid, USA) in the clinical sample of endotracheal aspirate, pleural fluid, and CSF with the absence of acid-fast bacilli in Ziehl-Neelsen (ZN) microscopy. The patient developed altered sensorium for 2 days with decreased speech and responsiveness and was unable to identify the attendants. This was followed by one episode of a generalized tonic-clonic seizure (GTCS) with a postictal loss of consciousness. The patient was intubated with GCS E3VTM5 with fentanyl sedation. Non-contrast computed tomography (NCCT) of the patient's head revealed frontoparietal variable densities and anisocoria. An ophthalmology consultation revealed a bilateral dot and blot hemorrhage. Meanwhile, an anti-EBV Immunoglobulin G test against viral capsid antigen (VCA) (tested outside) was found reactive and DNA was detected by real-time PCR in the blood by targeting the BNRF1 gene (Figure 2). Within a day, the patient had refractory septic shock, sudden onset bradycardia, and expired.

3 Discussion

The given case history, clinical manifestation, and investigation findings reasonably suggest that this patient was probably primarily infected by EBV in the past which eventually progressed to CAEBV/reactivation, leading to rare CNS complications as also reported previously (5). Rare CNS complications have been reported in 0.5% to 7.5% of cases and occur either as the sole or first clinical manifestation of primary EBV infection (5, 6). EBV has been well-documented to cause meningitis, encephalitis, myelitis, and vasculitis.

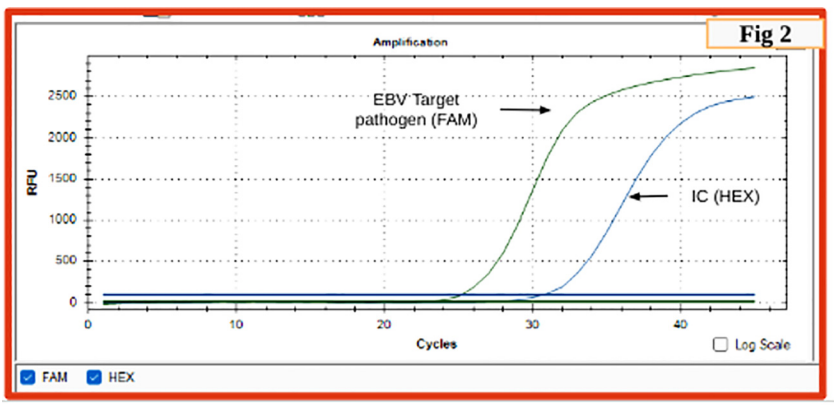

FIGURE 2
Real-time PCR graph indicating sigmoid graph at 25 cycles indicating positivity for EBV in the test sample (FAM) (cutoff is 35 cycles); sigmoid curve for internal control (HEX).

TABLE 2 A literature review of EBV co-infection with other pathogens.

S.No	Pathogen	Study population	Co-morbidities	Outcome	Pathogenesis	Ref
1.	*Cryptococcus*	Non- PLHIV	Immuno suppression due to Cushing's syndrome, sarcoidosis, hematological malignancies (leukemia or lymphomas), rheumatic disorders, Diabetes mellitus, cirrhosis, Hepatitis B, receipt of TNF inhibitors, organ transplant or rarely idiopathic low CD4 count	Increased mortality	Unknown	(3, 4)
		PLHIV	Immuno suppression due to HIV	EBV increases Cryptococcal meningitis	EBV lysate increases pro-inflammatory molecules and enhances the surface adhesion molecules expression which activates brain blood vessels endothelial cells leading to probable inflammatory Blood Brain Barrier (BBB) breach, thereby enhancing easy accessibility of EBV into the CNS.	(12, 13)
2.	Human Herpes Virus (HHV-6,8)	Patients with acute mononucleosis	None	EBV reactivation leading to full-blown disease	Unknown	(14, 15)
3.	Cytomegalovirus (CMV)	Patients with acute mononucleosis Immuno suppressive and Chemotherapeutic agent treatment	None	EBV reactivation	Unknown	(16, 17)
4.	Kaposi sarcoma associated herpesvirus (KSHV)	Patients with KSHV	None	EBV reactivation leading to enhanced tumorigenic potential	Alteration to gene expression (increased lytic gene activity)	(18, 19)
5.	Human papillomavirus (HPV)	Patients tested positive for HPV	None	EBV lytic reactivation	Oncogenes of HPV, E6 and E7	(20, 21)
6.	Human Immunodeficiency Virus (HIV)	People living with HIV and AIDS	Immunosuppression due to HIV	60-fold elevated risk of developing lymphomas	HIV-mediated immune dysfunction	(22, 23)
7.	COVID-19	Acute COVID infection	None	EBV reactivation	Unknown	(24, 25)
		Long COVID cases	None	EBV reactivation by COVID EBV increases the risk of developing long COVID	Unknown	(26, 27)

(Continued)

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TABLE 2 Continued

S.No	Pathogen	Study population	Co-morbidities	Outcome	Pathogenesis	Ref
8.	Syphilis	Patients with syphillis	None	Reactivates latent EBV	Toll-like receptor(TLR) 2/ B-cell receptor signaling-dependent manner	(28, 29)
9.	Tuberculosis	Allogeneic stem cell transplant recipients	Immunosuppression due to Transplant	EBV-associated polymorphic post-transplant lymphoproliferative disorders (PTLD) and CMV infection after transplant. Pulmonary and nodular TB	Unknown	(30, 31)
10.	*Helicobacter pylori*	Gastric Cancer	Immuno-compromised due to cancer	Progression of cancer	Increased interaction between the EBV's CagA protein and H. pylori promotes the activation of B lymphocytes passing through the stomach mucosa	(32)
		Chronic Gastritis (CGA) vs Non gastric diseases (NGD)	Chronic gastritis	Strong association between the simultaneous presence of H. pylori and EBV infection in CGA patients compared to NGD patients Higher dual prevalence of 54% in Chronic gastritis patients.	Co-infection has the potential to jointly alter the gastric mucosa, thereby influencing the clinical outcomes in affected individuals	(33)
11.	Malaria	Patients positive for malaria	None	*Plasmodium falciparum* activates latent EBV infection. Predisposition to Burkitts Lymphoma	Activation of latent EBV infection stimulate retinoid-responsive genes. This enhances viral replication and induces germinal center (GC) B cell expansion, activation-induced cytidine deaminase (AID) expression, and c-myc translocation, thereby predisposing to Burkitts Lymphoma	(34, 35)

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It is also known to cause various complications such as Guillain Barre Syndrome (GBS), acute demyelinating encephalomyelitis (ADEM), transverse myelitis, and polyradiculomyelitis (1, 6, 7). The nerve conduction test also established pure motor polyradiculoneuropathy. Although most individuals recover from primary EBV infection and enter into a virus-host balance state, leading to the healthy carrier stage, a small proportion has been reported to undergo further progression to CAEBV, hemophagocytic lymphohistiocytosis (EBV-HLH), diffuse B cell lymphoma, Hodgkin lymphoma, and other EBV-related natural killer/T cell lymphoproliferative-related diseases (1). In our patient, CAEBV appears a more likely possibility as it causes pancytopenia, decreased CD4+ T cell count, and HLH, and is evident clinically with coarse echotexture of the liver, splenomegaly, and prolonged fever (8). EBV has also been reported to stimulate primary $CD4^+$ T cells, resulting in many effector cells either dying or losing functional capacity and leaving a small proportion of effector cells to mediate protection during EBV persistent infection which has been found to have fallen as low as 0.33% (8). CAEBV is further substantiated with a reactive anti-EBV IgG test against VCA. CAEBV most likely resulted in encephalitis in this patient which could be substantiated by his predominant clinical features of memory impairment and focal neurological deficits of limb weakness and numbness, vestibule ataxia disorder, altered mental status, lymphocytic pleocytosis, and slightly elevated protein in CSF. There was no EBV investigation in CSF and the bacterial and fungal cultures and sensitivity tests provided a diagnosis of *Cryptococcus* and its treatment. This unfortunately leaves the exact cause of death unidentified as planning of the EBV diagnosis in CSF was left unattempted due to his death the very next day after confirming EBV in blood. This we consider a limitation in this case report. However, the various discussed investigations may be considered as reasonably establishing our hypothesis of a CAEBV-derived weakened immune system facilitating *C. neoformans* infection in this patient. Various earlier reports also report that EBV in conjunction with *C. neoformans* severely affects the CNS and other organs (3, 4). EBV has been reported to increase mortality in HIV-negative Cryptococcal meningitis cases (3). Our case report appears to be the first-ever case of coinfection of EBV and *C. neoformans* in an HIV-negative adult from Chhattisgarh and even from India.

We have presented this case to showcase the importance of clinical suspicion of EBV in cases of prolonged neurological deficit, pancytopenia, multiorgan involvement, bilateral pleural effusion, and splenomegaly. EBV encephalitis probably occurred due to direct viral invasion into neurons and endothelial cells of the brain blood vessels by increasing the pro-inflammatory molecules and enhancing the surface adhesion molecule expression, thereby creating a probable inflammatory blood-brain barrier (BBB) breach to augment *Cryptococcus* entry into CSF (3, 9). The immune injury to CNS could be caused by molecular mimicry between EBV and autoantigens of the CNS and antigen-antibody complex deposition (10). EBV encephalitis has also been reported earlier in HIV-negative adult patients with both mono and mixed infections (11). It is suggested that the antiviral ganciclovir targeting EBV along with corticosteroids and immunoglobulin could prove therapeutic benefits to these patients as also reported previously (12).

We have reviewed reported coinfections of EBV and found that EBV has been reported in conjunction with other viral, bacterial, fungal, and parasitic etiological agents such as Human Immunodeficiency Virus (HIV), cytomegalovirus (CMV), human herpes virus (HHV-6), severe acute respiratory syndrome (SARS-CoV-2), human papillomavirus (HPV), *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Treponema pallidum*, and *Plasmodium falciparum* to cause dual and triple infection (Table 2). EBV has been reported to undergo reactivation by enhancing lytic gene expression in presence of these different viral, bacterial, fungal, and parasitic agents (Table 1). The findings of EBV and *Cryptococcus sp* as the predominant pathogen in CSF and its more frequent occurrence than CMV in HIV patients have been reported previously (13).

This case report is concluded with a reminder of the utmost need for high clinical suspicion of EBV in unexplained neurological deficit disorders, pancytopenia, and multiorgan involvement along with screening for all possible bacterial and fungal etiologies.

Data availability statement

The datasets presented in this article are not readily available because no genetic sequential data was obtained. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

SN: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. GM: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. GS: Formal analysis, Investigation, Methodology, Writing – original draft. JS: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. AK: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fviro.2024.1485608/full#supplementary-material

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