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Review article

DEVELOPMENT OF LONG COVID AS A CONSEQUENCE OF THE COMPLEX RELATIONSHIP BETWEEN EPSTEIN-BARR VIRUS AND OUR IMMUNE SYSTEM

RAZVOJ PRODUŽENOG COVID-A KAO POSLEDICE KOMPLEKSNOG ODNOSA IZMEĐU EPŠTAJN-BAR VIRUSA I NAŠEG IMUNSKOG SISTEMA

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Abstract

Introduction: The pathophysiological development of long COVID (LC) is still insufficiently known. However, post infection fatigue syndromes were seen before, among other pathogens including Epstein-Barr virus (EBV). Considering EBV reservoir in COVID-19 patients, this review aims to present current knowledge related to EBV role in development of LC and with the potential diagnostic utility.

EBV infection: Following the primary lytic infection of epithelial oropharyngeal and nasopharyngeal cells EBV establishes a very complex mechanism of lifelong survival in B cells. Latent infection with occasional viral reactivations constantly challenges the host's immune response. In individuals with immune imbalance including COVID-19, it could drive long-term consequences.

EBV and COVID-19: The activity of EBV has been shown as the most prevalent human herpesvirus infection in COVID-19 population (41%). Correlation between lymphocytopenia-induced disability to remove the EBV, increases in EBV DNA viremia and COVID-19 complications have also been reported.

EBV and long COVID: The positivity of EBV DNA during acute SARS-CoV-2 infection predicted the presence of symptoms up to 60 days after COVID-19. Association between EBV infection and symptoms such as brain fog, fatigue, arthralgia and skin rashes have been also described in post infection sequelae ME/CFS. Anti-EBV early antigen-diffuse (EA-D) IgG antibodies were detectable among two-thirds of respondents experiencing LC. Increases in anti-EBNA1 IgG levels analyzed months following COVID-19 onset in convalescent LC population could serve as a potential marker of EBV reactivation at the time of acute SARS-CoV-2 infection. Some authors also managed to show anti-EBV viral capsid antigen (VCA) IgM seropositivity in half of COVID-19 patients indicating of either coinfection or EBV reactivation.

Conclusion: As a multisystemic illness, LC is without a defined spectrum of diagnostic and treatment options. Whereas EBV reactivation alone or together with other risk factors drives LC symptoms, further prospective studies involving different cohorts and tissue reservoirs are necessary to understand underlying biological mechanisms.

Keywords:
EBV,
SARS-CoV-2,
long COVID-19,
co-infection,
reactivation

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Sažetak

Uvod: Patofiziološki osnov razvoja produženog COVID-a (engl. *long* COVID - LC) još uvek je nedovoljno poznat. Međutim, sindrom zamora nakon infekcije viđen je i ranije, kod drugih patogena uključujući *Epstein-Barr* virus (EBV). Uzimajući u obzir rezervoare EBV kod pacijenata sa COVID-19, ovaj pregledni rad ima za cilj opis aktuelnih saznanja u vezi sa ulogom EBV u razvoju LC i sa potencijalnom dijagnostičkom implementacijom parametara EBV infekcije.

EBV infekcija: Nakon primarne litičke infekcije epitelnih orofaringealnih i nazofaringealnih ćelija, EBV uspostavlja veoma složen mehanizam doživotnog preživljavanja u B limfocitima. Latentna infekcija sa povremenim reaktivacijama stalno stimuliše imuni odgovor domaćina. Kod osoba sa imunološkim disbalansom, uključujući COVID-19, to može izazvati dugoročne posledice.

EBV i COVID-19: Aktivna EBV infekcija najrasprostranjenija je infekcija među ostalim humanim herpesvirusima kod COVID-19 pacijenata (41%). Takođe je prijavljena korelacija između nedostatka sposobnosti za regulaciju EBV izazvane limfocitopenije, povećanja EBV viremije i komplikacija COVID-19.

EBV i *long* COVID: Prisustvo EBV DNK tokom akutne infekcije SARS-CoV-2 pokazalo se kao prediktor simptoma do 60 dana nakon COVID-19. Povezanost između EBV infekcije i simptoma kao što su "moždana magla", umor, artralgija i osip na koži prethodno je opisana u postinfekcijskim posledicama ME/CFS. Anti-EBV EA-D IgG antitela pokazana su kod dve trećine LC ispitanika. Povećanje nivoa anti-EBNA1 IgG mesecima nakon početka COVID-19 u rekonvalescentnoj LC populaciji mogu poslužiti kao potencijalni marker reaktivacije EBV-a u vreme akutne infekcije SARS-CoV-2. Neki autori su takođe uspeli da pokažu seropozitivnost anti-EBV VCA IgM kod polovine pacijenata sa COVID-19 što ukazuje na koinfekciju ili reaktivaciju EBV.

Zaključak: Kao multisistemska bolest, LC je bez definisanog spektra dijagnostičkih i terapijskih mogućnosti. Dok reaktivacija EBV sama ili zajedno sa drugim faktorima rizika pokreće simptome LC, neophodne su dalje prospektivne studije koje uključuju različite kohorte i rezervoare tkiva u cilju razumevanja osnovnih bioloških procesa.

Ključne reči:
EBV,
SARS-CoV-2,
long COVID-19,
koinfekcija,
reaktivacija

Introduction

The pathophysiological mechanisms underlying the development of long COVID (LC) are still insufficiently known. Due to the most diverse spectrum of continuous or recurrent symptoms that interfere with the quality of life, intense efforts are continuously being made to understand them. As LC is generating an increasing burden on individuals and society with recognition in around 10 - 20% of people infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was identified as an emerging condition with an estimated 144 million individuals affected globally by October 2022 (1,2).

The World Health Organization (WHO) defined long COVID or post-COVID condition as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation (1). Among more than 200 symptoms, the most frequent include fatigue, brain fog, sleeping disorders, other cognitive symptoms, arthralgia, myalgia, pharyngitis, fever, headaches, gastrointestinal symptoms, skin rashes, depression, and anxiety.

Post infection fatigue syndromes were seen before, among other pathogens including Ebola virus, Epstein-Barr virus, Cytomegalovirus, Parvovirus 19, *M. pneumonia* and many more (3,4). Although inflammation is considered the main reason for these symptoms, the pathophysiological mechanisms remain unresolved. Therefore, treatments are primarily based on symptom relief and supportive care (5). With characteristic neuroinflammation and inability of individuals to perform basic tasks of work or daily living, it is not difficult to notice the similarity between LC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (6). Firstly like LC, it is associated with previous viral infection and usually in healthy and active individuals (7). Secondly, chronic nature and presentation of both conditions are similar.

The host defense represents the main role of immune response in acute viral disease. However, immune system might be involved in other non-specific processes. Those include critical immune dysregulation, triggering the autoimmune development or disability to control persistent latent infections (3). Thus, SARS-CoV-2 persistency or reactivation of human herpesviruses (HHVs), especially Epstein-Barr virus, could represent the link connecting all the mentioned consequences (8).

Considering possibilities of activation of EBV reservoir in patients in COVID-19, this review aims to present a cross-section of current knowledge related to EBV role in development of LC and the potential diagnostic utility of EBV infection activity parameters.

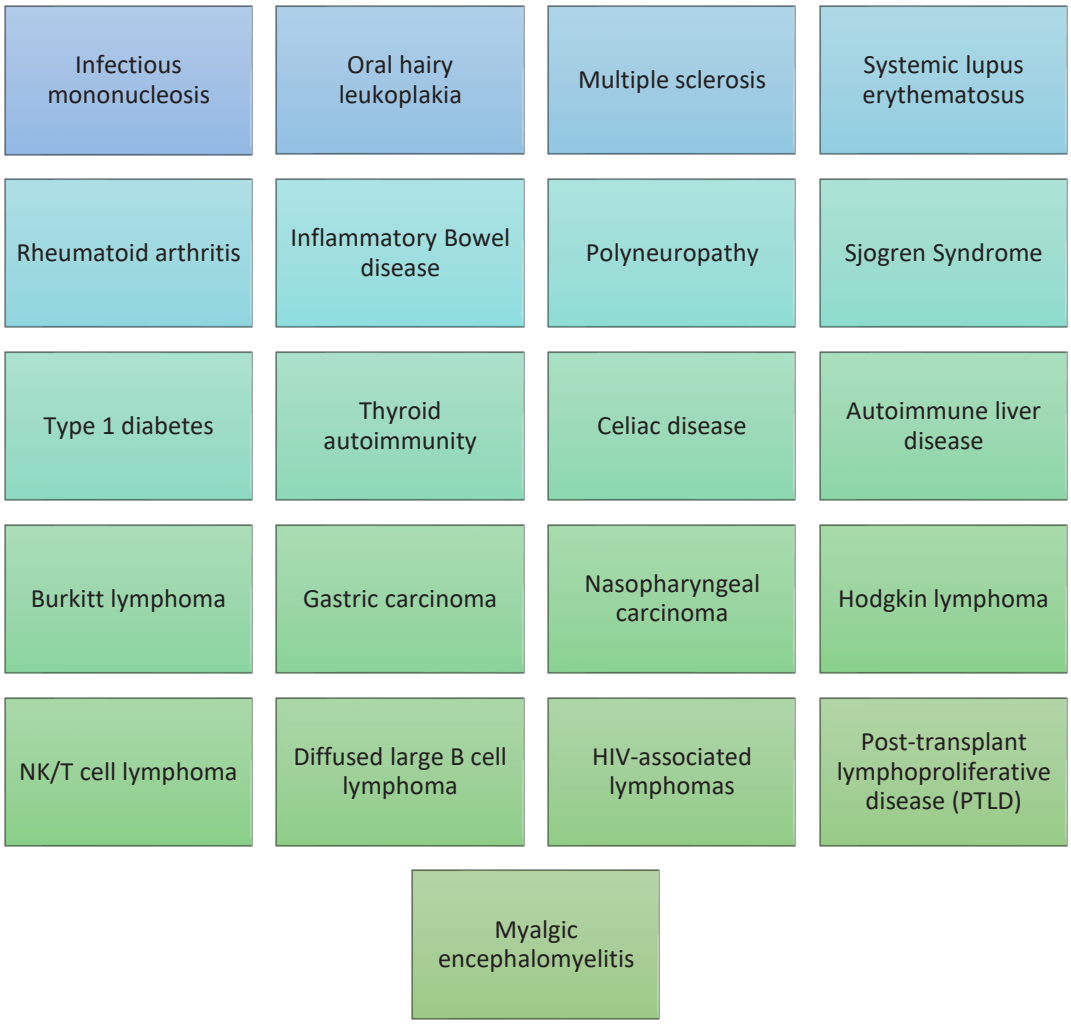

Figure 1. List of Epstein-Barr virus associated diseases.

Epstein-Barr virus infection

The Epstein-Barr virus (EBV) is a double-stranded DNA ubiquitous virus that latently infects up to 99% of the world's population. It is also known as human herpesvirus 4 (HHV4), member of the gammaherpesvirus family. As the first identified human tumor virus, it was found to be associated with the wide spectrum of human tumors: lymphomas, NK and T cell lymphoproliferative diseases, nasopharyngeal carcinoma, post-transplant lymphoproliferative disease (PTLD), gastric carcinoma etc. (9). Moreover, EBV is also linked with infectious mononucleosis, oral hairy leukoplakia, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis (**figure 1**). Primarily, route of EBV transmission occurs through saliva, however, it could also be transmitted through breast milk, bodily fluids, and transplantation of EBV-positive organs (9).

Following the primary lytic infection of epithelial oropharyngeal and nasopharyngeal cells EBV establishes very complex mechanism of lifelong survival in B cells. Latent infection characterized with limited gene expression and occasional viral reactivations constantly challenges the host's immune response (10). Those shifts between a latent state and active lytic cycle are observed in a variety of stimuli, including immunosuppression, other infections, or psychological stress (11). Lytic replication commonly leads to cell death and spread of mature virions. Additionally, abortive lytic expression could also develop in cases where the virus expresses a sub-set of lytic genes without achieving complete lytic replication (12).

In a healthy immune system, the impaired control of EBV latency is rare. However, in a reduced efficiency of T cells and expansion of EBV-infected B cells in immunocompromised individuals or in those with the triggered immune disbalance by COVID-19, it could drive long-term consequences (3, 13). Moreover, immune evasion by EBV itself had been described at both innate and adaptive immunity response levels. It downregulates activation of several pattern recognition receptors (PRRs) including TRAF6, TLR9, NLRP3 and others (9). It also modulates RLR-mediated signaling through the mitochondrial adaptor protein, reduces interferon signaling, prevents interferon (IFN) induction and targets DNA sensing pathways (9). Evasion of adaptive immunity includes inhibition of MHC class I and II presentation by ubiquitinylating induced internalization, degradation of HLA-A and HLA-B and prevention MHC class II antigen presentation to T cells (9). In addition, EBV prevents proteasomal degradation and presentation to T cells, preserves infected B cells from NK-cell mediated destroying, NK cells from killing EBV-infected B cells and CD8 T cell recognition of EBV-infected B cells (9).

Epstein-Barr virus and COVID-19

According to literature data, EBV activity has been shown as the most prevalent human herpesvirus infection in individuals with COVID-19 (41%) (14). Even higher rate of EBV co-infection could reflect high EBV frequency in the general population, it's involvement in the evolution of diversity of lymphoproliferative diseases, carcinomas and autoimmune diseases, still requires special attention. That is why reports of increased number of complications and mortality rates found in COVID-19 patients with coexistent EBV and SARS-CoV-2 infection represents significant findings (14). Correlation between lymphocytopenia-induced disability to remove the EBV, increases in EBV DNA viremia and COVID-19 complications have also been reported (15). Thus, in behalf of frequently developed lymphocytopenia in COVID-19 individuals, some authors, as very important, advise excluding SARS-CoV-2 and EBV co-infection, mostly in the elderly or patients after transplantation, who are susceptible to both infections (16). In addition, measuring of EBV viremia as early as at initial COVID-19 diagnosis was defined as of fundamental importance for understanding post-acute COVID-19 sequelae (PASC) and introducing antivirals early in the disease course or even developing new treatment (17).

Among previous publications that reported EBV and SARS-CoV-2 co-infection there were different manifestations in patients: lymphoproliferative disorders, lymphadenopathy, splenomegaly, skin rash, polyneuropathy and infectious mononucleosis. On the other hand, COVID-19 patients also presented various comorbidities: transplantations, myocarditis, cardiovascular diseases, fatigue, multisystem inflammatory syndrome in children (MIS-C) (14).

Epstein-Barr virus and long COVID

Based on publications available so far, the role of EBV infection in defining risk factors for the severity of COVID-19 outcomes is still being investigated. One of the recent reports has demonstrated that EBV DNA positivity during acute SARS-CoV-2 infection represented the predictor for the presence of symptoms at up to 60 days after COVID-19 (17). On the other hand, the role of EBV is indisputable on the evolution of previously mentioned post infection sequelae such as ME/CFS. It is interesting that the first data about this syndrome could be found in patients after infectious mononucleosis (IM) (18). Thus, symptoms such as brain fog, fatigue, arthralgia and skin rashes are not exclusive for long COVID-19 patients. It was suggested that the synergistic destruction and disruption of pathways in cells and mitochondria during EBV and SARS-CoV-2 co-infection drive described sequelae (11). Both viruses have capacity to induce p53 degradation, alter metabolic profile and mitochondrial biogenesis. As diseases are associated with an inflammatory response, increased cytokine activation correlates with disease severity and patients might struggle with growing infections burden over time. Therefore, EBV-associated fatigue could be developed in previously compromised patient (**figure 2**) (19,20).

When it comes to available serological data, anti-EBV early antigen-diffuse (EA-D) IgG antibodies were detectable among two-thirds of respondents experiencing LC (21). Anti-EBV EA-D IgG levels were even higher in those with multiple LC presentations, indicating that recent EBV activity, could be trigger for LC. It is known that those antibodies represent recent viral activity and lytic replication in period 3 to 6 months before measuring (22).

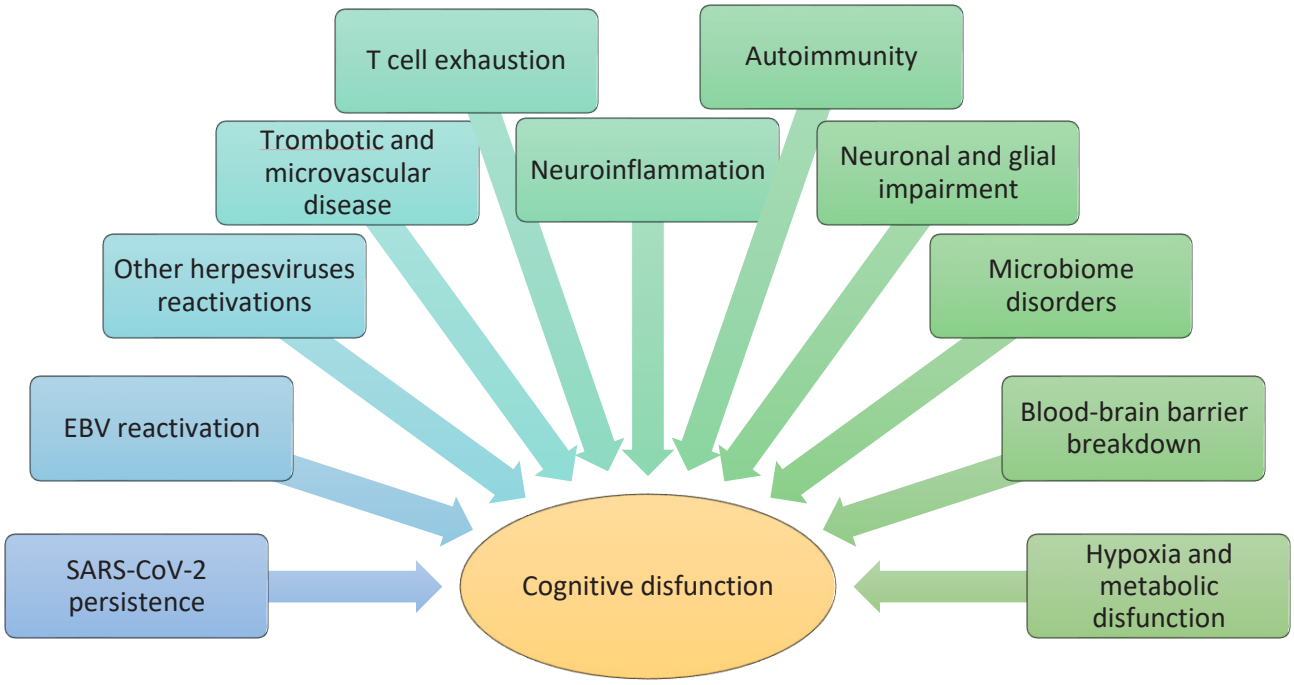

Figure 2. Epstein-Barr virus infection and other possible factors that contribute to central nervous system impairment in long COVID.

In LC patients at a median of 4 months after diagnosis, association was reported with positivity and elevation of anti-EBV EA-D IgGs (22). Even this marker is not necessary for the development of sequelae, it is most strongly associated with fatigue among reported symptoms, but less so with other like cardiopulmonary and gastrointestinal symptoms.

Immune response after primary EBV infection elicits life-long anti-EBV nuclear antigen 1 (EBNA1) IgG antibodies. Their titers might be increased during transition between the lytic and latent stages of EBV infection (23). Thus, it was proposed that increases in anti-EBNA1 IgG levels analyzed months after COVID-19 onset in convalescent LC population could serve as a potential marker of EBV reactivation or other inflammatory insult at the beginning of SARS-CoV-2 infection (22). In addition, EBNA1 was described as the target for molecular mimicry with potential stimulation of autoreactive antibodies. Cross reactivity between EBNA1 and glial cell adhesion molecules has been already suggested in pathogenesis of multiple sclerosis (24). Thus, high levels of anti-EBNA IgG antibodies might drive aberrant autoimmune responses that would additionally explain potential mechanism of LC (22). As in myalgic encephalomyelitis/chronic fatigue syndrome there is also the possibility for a cellular compartment expanded in COVID-19. Elevation of anti-EBNA IgG titers resulted from nonspecific hypergammaglobulinemia could evolve during acute viral infections or from circulating latently EBV-infected memory B lymphocyte burden (25).

Some authors also managed to show anti-EBV viral capsid antigen (VCA) IgM seropositivity in half of COVID-19 patients indicating of either coinfection or EBV reactivation (26). Moreover, those seropositive patients were three times more likely to develop fever than those without detectable EBV reactivation. Finally, seropositivity of EBV envelope glycoproteins gp42 and gp350 have also been reported (27). They are necessary for EBV lytic infection of B lymphocytes, but also represent the targets for neutralizing antibodies. As their presence in circulation might be short-lived, it could be assumed that before the development of LC recent viral activity could be present (22).

One of the studies investigated EBV DNA as the potential risk factor for developing LC (17). They found that EBV viremia at the time of COVID-19 diagnosis was one of the four predictive factors for LC development. As the same research group observed cytomegalovirus DNA and SARS-CoV-2 RNA presence, persistent symptoms of long COVID like fatigue and chronic sputum overproduction were specifically associated with Epstein Barr virus viremia.

As inflammation was defined as the most prominent feature of COVID-19, some mechanisms that help EBV reactivation may also be explained by this process. Acute SARS-CoV-2 infection with exposure to viral antigens robustly activate the NLRP3 inflammasome (28). Therefore, stimulation of NLRP3 inflammasome leads to the synthesis of IL-1β and occasionally pyroptosis. Moreover, this activation could also drive EBV reactivation (29, 30). It is further possible that reactivated EBV could be the consequence of other mechanisms such as through the off-target outcomes of remdesivir, gut microbiota dysregulation leading to elevated butyrate production, or XBP1 activation (28). It is obvious that more research is needed to clear the link between EBV reactivation and post-acute syndrome.

In addition to HHV-driven pathophysiological processes and even bioenergetic and metabolic alterations of the infected cell, SARS-CoV-2 itself induces immunosuppression or immune dysregulation. This enables latent viruses moving to the central nervous system (CNS), providing conditions for neuroinflammation which could also explain some of the symptoms. In addition to long COVID presentation, such processes have been described in recent years in biology of human herpesviruses infection in Alzheimer's disease (3). Finally, some authors define this sequence of events a "multiple hit model", where activity of one pathogen could support the virulence of the next. By modifying human gene expression, initial pathogen such as SARS-CoV-2, leads to functional redundancy (6).

The „new", third state of EBV gene expression has been lately proposed by the accumulating data. A conventional concept defines either latency or lytic replication, but abortive lytic/leaky replication may contribute to EBV-associated malignancy development and ME/CFS (18, 31). Moreover, in this case the presence of an active EBV infection may not always be followed by increasing of viral load or typical serological observations. On the other hand, there are increasing levels of anti-herpesviruses deoxyuridine triphosphate nucleotidohydrolase (dUTPase) antibodies, a defective EBV-specific B and T cell response, and a positive upregulation of EBV-induced gene 2 (EBI2) messenger RNA (mRNA) in peripheral blood mononuclear cells (18, 32). All of the above could contribute to the chronic innate response and symptomatology of LC which has been already described in ME/CFS (33). Therefore, in line with the presented model, LC develops in three steps: first, SARS-CoV-2 infection of "weak" HLA-II haplotypes immune system, an acquired immunodeficiency develops against SARS-CoV-2 and/or EBV which prevents control of latency I cells; second, ectopic EBV-latent lymphoid reservoirs including those in the central nervous system promote inflammation and further impairment of cell-mediated response; and third, chronic exposure to viral antigens drives immune exhaustion and the disease consolidates (33).

Conclusion

Long COVID is a multisystemic illness already debilitated millions of people. Diagnostic and treatment options are still insufficient. Whereas EBV reactivation alone or together with other risk factors that disrupt the normal functions of the immune response drive LC symptoms, further prospective studies involving different cohorts

and tissue reservoirs are necessary to understand underlying biological mechanisms. Previously proven association between positivity of EBV infection markers and occurrence of LC symptoms could guide consideration of its implementation into a diagnostic panel or screening. Therefore, to address potential diagnostic and treatment options, diverse clinical trials are urgently needed.

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