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Mode of infection and some diseases caused by Epstein Barr virus: The most ubiquitous, common malignant and characteristic virus

Abstract

Epstein Barr virus (EBV) was detected for the first time by electron microscopy (EM) in a malignant Burkitt's lymphoma. EBV has a worldwide distribution and its prevalence is more than 90%. It is a malignant virus, symptoms vary from mild or find no symptoms in some individuals and serious symptoms or cancers in others. EBV is a characteristic one since it has a lot of properties to become latent and modulate the host immune system in a serious manner in some conditions where it has many proteins having sequence and functional homology with many human proteins. EBV could be transmitted through saliva or contact with the air borne, blood transfusion, organ transplantation semen or cervical secretions. EBV Causes a lot of diseases which varies according to some factors. Rediagnosis For COVID-19 is recommended by considering it EBV or ovine herpes virus 2 (OvHV-2) where I think that they are the same virus With two names according to human or veterinary medicine because accurate diagnosis is the first and most important step for controlling COVID-19 and I show that the obtained RNA and considered as corona Virus is mainly one of the messenger RNA (s) of EBV (0vHV-2) to be translated for proteins demanded by this herpesvirus. This false diagnosis may be performed with other RNA viruses named previously. Proper diagnosis will be achieved by electron microscopy for detection of herpes viral particles and sequencing of glycoprotein B complete gene. Another recommendation is taking in consideration that stool is among routes of infection as well as milk and colostrum with special care during management for all animals or birds (because all species are susceptible) which also give good chance for experimental application of vaccines, antibodies as well as studying pathogenesis and pathology of the virus.

Keywords: Epstein Barr virus, autoimmune diseases, cancer, infectious mononucleosis, chronic fatigue syndrome, chronic active EBV

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Introduction

Epstein Barr virus (EBV) is a DNA virus belongs to the family her Herpesviridae and subfamily gamma herpesvirinae and is known as human herpesvirus 4. Its composition is a linear ds DNA genome enclosed by a capsid of icosahedral symmetry which is surrounded by the tugment then a host cell membrane - derived envelope embedded by glycoproteins .[1] It was detected for the first time by electron microscopy in a malignant Burkitt's lymphoma .[2]

EBV is ubiquitous and common virus

EBV has worldwide distribution[3]. About 98% of adults are shown to be infected with EBV.[4] Developed countries which have high hygienic measures, seroconversion of EBV peaks in children of 2 - 4 years as well as 14 - 18 years where there is gradual increase with age, approximately 0 - 70 % at childhood to reach more than 90 % for adults [5] but countries having poor hygienic measures, EBV infection occurs in early childhood and nearly all children are seropositive when they are 6 years.[6]

EBV is a malignant virus

Most individuals carrying EBV have no effects from infection.[7] Where infection with EBV is usually without symptoms, flu-like symptoms or giving symptoms as in case of infectious mononucleosis[8] and EBV - associated venous thromboembolism which often appears in immunocompromised patients.[9] Also, EBV primary infection in children is mainly undistinguishable from other viral diseases and some patients develop non - painful growth of lymph tissue.[10] However, researchers still try to know why EBV causes mild or even no signs in most infected individuals but in the other hand, it is linked to cancer in others.[11] Stress,[12] age of individual catching infection with EBV, genetic susceptibility , factors of the environment and presence of other pathogens effect on development and type of symptoms.[11]

EBV is a characteristic virus

EBV possess many proteins having sequence and functional homology with many human proteins. They have important role in the control of EBV infected cells.[10] EBV codes a cytokine and a cytokine receptor which are very important for modulating the immune system for allowing the persistent infection. BCRF1 protein of EBV is a homologue for the host interleukin 10 (IL-10) for allowing the viral persistence leading to inhibition of interferon gamma synthesis[13] in addition to stimulation of mast cells proliferation and inhibition of macrophage inflammatory chemokine production.[14] BARF1 protein of EBV is a homologue for the host colony stimulating factor 1 for acting as a decoy receptor leading to cytokine action blocking which results in the inhibition of interferon 2 alpha expressed by monocytes. So, BCRF1 and BARF1 proteins of EBV help for evading the immune response during the acute infection with EBV help for evading the immune response during the acute infection with EBV or the reactivation of EBV in latently infected cells.[13] EBV possess two homologues for the host b c l-2 , BHRF1 and BALF1 which play role in cell immortalization mechanism by apoptosis inhibition.[15]

The activated cytotoxic T cells help for some signs of EBV infections such as IM due to cytokine secretion like gamma interferon in addition to IL-2 (10). However, IL-15 which is the same family

receptor for IL-2 if expressed dysregulately by its production in excess and consequently tissue necrosis factor alpha (TNF-α) leads to stimulation as well as maintenance of cytotoxic activity for T cells in addition to natural killer (NK) cells leading to auto-destruction of the host tissue.[16]

Since cytokines mediate the innate immune response, sustained activation and/or dysregulation of the innate immune response participating for the pathogenesis of some conditions such as chronic inflammatory disease, cancer or congestive heart failure.[17] An important example is the severe chronic active EBV (CAEBV) which is considered a clonal expansion of T or NK cytotoxic cells. Associated with this clonal expansion, a clonal anomalies of EBV genome may occur leading to frequent development in T lymphoma. Patients with T or NK cells disease are shown to have high levels of pro - and anti - inflammatory cytokines such as IL -1 beta , interferon gamma , IL-13 , IL - 15 , TNF-α and transforming growth factor beta.[18] EBV nuclear antigen 1 (EBNA - 1) efficiently can tether the DNA of the virus to the host chromosomes. So, the both can be duplicated during mitosis and given for the daughter cells.[19] Therefore, EBV remains mainly latent in the infected host. During latency in infected B lymphocytes, EBV DNA is highly methylated[20] which results in inhibition for the lytic genes expression. EBV was considered the first virus in which micro RNA (miRNA) was detected in the nucleus of different cell lines of Hodgkin's and Burkitt's lymphoma[21] where miRNA are short (18-30 nt) non coding RNA molecules control expression of viral and cellular genes.[22] EBV can infects B cells, epithelial cells, natural killer (NK) cells, natural killer T (NK/T) cells, macrophages, monocytes and myocytes.[10]

Mode of infection by EBV

Exchange of saliva or contact with the airborne virus are the main methods for first exposure for the virus before or after adolescent ages.[23] Blood transfusions and organ transplantations are among the possible ways for transmission[3] although the respiratory tract is the main way for EBV infection. However, EBV presence in secretions of cervix, semen in addition to genital mucosa is detected.[10]

Some diseases caused by EBV

Infectious mononucleosis (IM): EBV causes IM which is a lymphoproliferative disease of self-limiting and it is characterized with extensive T cell activation. Its reactivation during immunosuppression usually shown to be associated with oncogenesis.[24] IM results from infection of adolescents and young adults with EBV results in fever (2 to 3 weeks), pharyngitis with exudate in 30% of patients in addition to cervical adenopathy's. Patients show weakness, fatigue, anorexia, headache in addition to fever during the prodromal phase. Splenomegaly is detected in more than 17 % on physical examination and in 100% of patients on radiological examination. Infrequently, obstruction of the air ways, abdominal pain, rash, jaundice, hepatosplenomegaly and eyelid edema occur. 5% of patients develop cutaneous lesions and rash is macular petechial, scarlatiniform, urticariform or erythematous multiform. However, more than 90% of patients taken ampicillin 10 days ago, develop maculopapular exanthema.[10] Initial presence of acute myocarditis and large - vessels arteritis in case of IM caused by EBV is rare but recorded.[25]

Complications for IM: Complications of IM include neutropenia, thrombocytopenia, rupture of spleen, obstruction of air path way due to tonsillar hypertrophy, impairment of the central nervous system as well as fulminant hepatitis.[10]

Chronic fatigue syndrome (CFS): Patients with cured acute IM caused by EBV were examined six months after being cured for detection of disorders which may result and known as chronic fatigue syndrome (CFS).[26]

Physiologically, immunological control helps to make the percentages of infected cells as low as possible but in some cases such as immunosuppression, EBV will be reactivated and enters again the lytic phase.[10]

Chronic active EBV: Some patients show recurrent symptoms of IM more than six months to give condition called chronic active EBV (CA EBV) infection and it is also a lymphoproliferative disorder[10] where patients usually have fever, hepatic dysfunction and splenomegaly. About 50% of patients present lymphadenopathy, thrombocytopenia and anemia. However, 20 to 40 % of patients present signs of hypersensitivity to mosquito bites (HMB), rash, hemophagocytic syndrome in addition to coronary artery aneurysm. Sometimes, patients have basal ganglia calcification, oral ulcers, lymphoma in addition to interstitial pneumonia as well as central nervous system disease. Thrombocytopenia appears in 8 or more years old patients with worse prognosis if there is also infection of T cells with the virus. However, death may be due to hepatic failure, malignant lymphoma and other infections.[18]

EBV can cause many diseases for cutaneous tissue which are acute and chronic ones. Infectious mononucleosis rash and Lipchutz ulcers are among the acute ones but chronic conditions are like HMB, hydroa vacciniform (HV), hydroa vacciniform - Type T - cell lymphoma (HV TL), nasal and extra - nasal NK/ T - cell lymphoma.[10]

HMB caused by EBV: HMB is a disease associated to EBV chronic infection as a cutaneous local reaction appears as erythema, blisters ulcers in addition to scar tissue formation which are followed by systematic signs such as fever, lymphadenopathy, hepatic dysfunction as well as hemophagocytic syndrome following mosquito bite. NK cells and TNK cells are the target cells for EBV latent infection[27] Sometimes HMB is accompanies by visual hallucinations. The skin lesions present vasculitis.[28] Death of some patients due to hemophagocytic syndrome or lymphocyte proliferative disorders.[29]

HV caused by EBV: HV is a childhood photosensitive dermatosis caused by EBV - infected T cells of 3 to 20% of dermal filtrate and lesions occur on the photo exposed parts such as cheeks, ears, nose, hands in addition to forearms.[30] Sometimes, severe lesions may result and saddle nose is an example due to bone or cartilage resorption.[31]

HVLLT caused by EBV: HVTL resembles HV but it is more extensive and usually followed by fever, lymphadenopathy, hepatosplenomegaly and liver enzymes elevation as well.[30]

Extranodal NK/ T-cell lymphomas: Extranodal NK/T-cell lymphoma, nasal type is a rare aggressive non Hodgkin lymphoma. Its origin is nasal cavity or paranasal sinuses as a destructive nasal lesion of vascular damage in addition to prominent necrosis.[32] Extranasal places are skin, respiratory and gastrointestinal tracts and testicles as well presenting necrosis due to vascular damage.[33]

Hemophagocytic syndrome (HPS): Hemophagocytic syndrome (HPS) associated with infection with EBV is characterized by engulfment of red blood cells (RBCs) or platelets by macrophages.[34]

Coagulopathy caused by EBV: EBV pathogenesis may result in over activation of T cells and macrophages leading to over production of cytokines, causing fatal coagulopathy +/- central pontine myelinolysis which are considered as most dangerous form.[35]

Cancers caused by EBV: EBV still the first human virus involved directly to lymphoid and epithelial tumors oncogenesis.[36] EBV in some individuals is linked to different cancers such as Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, gastric adenocarcinoma, leiomyosarcoma and breast cancer as well.[7] EBV is also linked to post transplant lymphoproliferative disorders (PTLDs) which are considered among the most common malignancies following transplantation.[3]

Autoimmune diseases caused by EBV: EBV has been detected to be linked to autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), inflammatory bowl disease (IBD), celiac disease, systemic lupus erythematosus (SLE) and type 1 diabetes.[11]

A link between B cell - tropic EBV and onset of MS was demonstrated where mononucleosis was shown to be predisposing to it and EBV was detected in MS brain.[37] However , other previous studies detect a link between EBV and development of systemic autoimmune diseases (SADs) where uncontrolled EBV infection can promote development of autoreactivity's, diversion in persons who are genetically susceptible giving some symptoms according to the genetic background and reactivation site.[38] Also, patients with refractory celiac disease present EBV in their enterocytes and inflammatory cells.[39]

Vasculitis: Central nervous system (CNS) vasculitis in addition to myelopathy are considered neurologic symptoms of EBV - T / natural killer -cell lymphoproliferative disordered affecting children.[40] Also, Kawasaki disease (KD) which is an acute systemic vasculitis in addition to other signs could be triggered by EBV.[41]

Recommendation

Re - diagnosis for COVID-19 is recommended by considering it EBV or ovine herpesvirus 2 (OvHV-2) where I think that EBV and OvHV-2 is the same virus with 2 names according to human or veterinary medicine since accurate diagnosis is the first and most important step for COVID-19 control because I show that the obtained RNA which considered as corona virus is mainly one of the messenger RNA(s) of EBV (OvHV-2) to be translated for proteins demanded by this herpesvirus. This false diagnosis may be performed with other RNA viruses named previously. Proper diagnosis will be achieved by electron microscopy to detect herpes viral particles and sequencing of glycoprotein B complete gene. Another recommendation is taking in consideration that other infection routes is through stool as well as milk and colostrum and caring during management with all animals or birds where all species are susceptible hence, they give a good chance for experimenting vaccines, antibodies (polyclonal, monoclonal or heavy chain) or drugs after infection of healthy animals or birds as well as naturally infected ones in addition to study pathogenesis and pathology of the virus.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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