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An oncogenic Epstein Barr virus developing diseases and cancer in human

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Abstract

Epstein Barr virus is a ubiquitous virus infecting almost entire population of the world usually completely unnoticed. Nevertheless, despite lifelong latency in human the virus develops diseases in only a few of them. The diseases developed by the virus ranges from infectious mononucleosis to the cancerous Burkitt's lymphoma. Further, this is also observed that the diseases developed by the EBV infections have always been influenced by the genetic as well as environmental factors including immunity disorders and the age of an individual. The present paper deals with the study of Epstein Barr virus causing several diseases including cancer in human.

Keywords: Epstein Barr virus, Mononucleosis, EBV reactivation, Cancer, Burkitt's lymphoma.

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INTRODUCTION

Burkitt's lymphoma was observed and indentified for the first time by a British surgeon Denis Parsons Burkitt among the children of Africa in 1956 (Burkitt 1958) [1]. Similarly, Epstein Barr virus (EBV) is investigated by Anthony Epstein, Bert Achong and Yunne Barr in 1964 as a new human oncovirus from Burkitt's lymphoma (Epstein 1964) [2]. This is highly aggressive B-cell Hodgkin lymphoma (NHL) and a kind of herpes virus containing enveloped large double stranded linear D.N.A. genome. This is also known as human gammaherpesvirus-4, HHV-4 or Burkitt's lymphoma virus belonging to the family *Herpesviridae* and the genus *Lymphocryptovirus*. This is a DNA tumor virus infecting B-cell of the immune system and epithelial cells (Epstein 2005) [3]. These infections are quite known in the society as "kissing disease", glandular fever, mononucleosis or in short "mono". The disease is very easily transmitted simply either by kissing or coughing, sneezing, sharing drinking or eating utensils and genital secretions. As with other herpes viruses, though, not everyone develops the symptoms of kissing disease, their infection is lifelong. Similarly, the prominent period of getting infection has been found to be the early teenage. The EBV in human causes harmless to life threatening infections causing cancer. These cancers are most common in Africa and southeast Asia (Thompson and Kurzrock 2004, Bravender 2010 and Mark *et al.* 2016) [4-6]. The present paper deals with the study of Epstein Barr virus causing diseases and cancer in human. The author has gone through several original research papers in order to explore the facts regarding the viral origin of cancer.

Clinical Presentation

Epstein Barr virus is one of eight known human herpes viruses especially affecting the teenagers has got lifelong latency in the host. Approximately, 50 % of children are being infected with the same virus during their childhood. This is evidenced by the fact that more than 50 % of adults have their previous infections. And, rest of the individuals who have never been exposed earlier, if infected with the EBV in future may also suffer from infectious mononucleosis. In addition, it has also been observed that the mono developed in adulthood are found to be rather more problematic, painful and having complications than their childhood (Jensen 2000, Pattle and Farrell 2006, Wolfgang and Paul 2004 and Gulfaraz *et al.* 2014) [7-10].

Mononucleosis has the incubation period of 2 to 6 weeks and the symptoms are as sore or strep throat, swollen tonsils with strep infections mimicking as tonsilytis, cough, swollen glands with fever, fatigue, malaise, muscle aches, headache, swollen lymph nodes especially of neck (Shannon and Rowe 2014 and Mark *et al.* 2016) [6, 11]; lymphadenopathy (Weiss and Malley 2013) [12]; splenomegaly (Eapen 1999) [13]; enlarged liver mimicking as hepatitis (Evans 1948) [14]; atrial fibrillation (Aghenta *et al.* 2008) [15]; increased lymphocytes, abonormal B cells and thrombocytopenia (Tsimberidou *et al.* 2006) [16].

Further, the specific diagnostic tests for mononucleosis are agglutination monospot test and the heterophile antibodies tests as IGM for acute infection and IGG for chronic infection (Elgh and Linderholm 1996 and Dave *et al.* 2006) [17, 18]. Similarly, in patients with Burkitt lymphoma the monospot test is positive

and tissue biopsy gives a characteristic starry sky appearances (Elgh and Linderholm 1996 and Yang *et al.* 2020) [17, 19].

Geographical Distribution

The most common type of carcinoma caused by the Epstein Barr Virus is Burkitt's lymphoma (Pannone *et al.* 2014) [20]. Mainly three types of Burkitt's lymphomas have so far been reported; they are endemic, sporadic and the immunodeficient type. While endemic type of Burkitt's lymphoma is confined to the region of central Africa, the non African type occurs sporadically in rest of the world. The endemic central African type of Burkitt's lymphoma sometimes also linked with malaria is characterized as the non-Hodgkin Burkitt's lymphoma developing extremely painful unilateral enlargement of the face mostly affecting cheek and mandible where hospitalization becomes absolutely necessary for airways compromisation in difficult breathing (Thorley Lawson 2016) [21]. On the other hand, the non-African type of Burkitt's lymphoma occurs sporadically in other parts of the world usually affecting the ileoceacal region of the abdomen. Similarly, the Burkitt's lymphoma has also been reported to occur in some immunocompromised or immunosuppressive patients (Brady *et al.* 2007, Molyneux *et al.* 2012, Corvalan *et al.* 2019 and Yang *et al.* 2020) [19,22-24]. So, how does Epstein Barr virus cause the disease differentially in different parts of the world is a matter of further research.

Pathogenesis and Oncology of the Virus

Further, EBV contributes to the pathogensis of several diseases and cancer in human such as malignant lymphoproliferative diseases (Rezk *et al.* 2018) [25], Burkitt's lymphoma (Pannone *et al.* 2014)[20], Hodgkin's lymphoma (Altschuler 1999 and Gandhi *et al.* 2004)[26,27], B & T cells lymphoma (Coleman *et al.* 2018)[28], hemophagocytic lymphohistiocytosis (Marsh 2018)[29], gastric carcinoma (Yau *et al.* 2014)[30], breast cancer (Joshi *et al.* 2009 and Bae and Kim 2016)[31,32], nasopharyngeal carcinoma (Dogan *et al.* 2014)[33], acute renal failure (Lei *et al.* 2000)[34] and EBV and childhood disorders like Alice in wonderland syndrome (Mastria *et al.* 2016)[35] and acute cerebellar ataxia (Nussinovitch *et al*. 2003)[36]. Similarly, based on some evidences the higher risk of certain autoimmune diseases are also developed with the infection of EBV, some of them are as dermatomyositis (Anette *et al.* 2013) [37], systemic lupus erythematosus (Gionanlis *et al.* 2009 and Anette *et al.* 2013)[37,38], rheumatoid arthritis (Bonneville *et al.* 1998 and Anette *et al.* 2013)[37,39], Sjogren's syndrome (Altschuler 1999)[26], multiple sclerosis (Ascherio and Munger 2010, Mecheli *et al.* 2015 and Hassani *et al.* 2018)[40-42] and the diseases developed in immunosuppressive or immunocompromised patients in association with EBV are hairy leukoplakia (Razia *et al.* 2016) [43], CNS lymphomas (Kitai *et al.* 2010) [44], acute cerebellar ataxia (Nussinovitch *et al.* 2003 and Stephanie and Bruce 2019) [36,45], Kikuchi's disease (Gionanlis *et al.* 2009)[38], Smooth muscle tumors (Magg *et al.* 2018)[46], Stevens Johnson's syndrome (Brunet *et al.* 2013[47], subepithelial infiltrates (Matoba and Jones 1987)[48] and new daily persistent headache (Hamada *et al.* 1991)[49].

EBV has been found to be implicated in the pathogenesis of human malignancies via genomic instability and chromosomal aberrations to the development of variety of cancers in human (Kamranvar *et al.* 2007) [50]. One of them as Burkitt's lymphoma has always been found to be associated with Epstein Barr virus. This is rapidly growing tumor of B cells and macrophages where malignant chromosomal translocations between 8 to 14 chromosomes in an individual. Basically, EBV infects the white blood cells called the lymphocyte B cells. The virus, in fact, does not replicate in the same cells, instead, it transforms them into immortal lymphoblasts having indefinite lifespan (Borncamm *et al.* 1987, Thorley Lawson 2001 and Martin 2009) [51-53]. In addition, EBV latent viral genes LMP1 and LMP2 play a major role in modulating the telomere dysfunction and DNA damage (Liu 2004 & 2005 and Chen *et al.* 2005) [54-56].

Treatment of the Disease

As mononucleosis mostly affects the teenagers and young adults, it gets better without any treatment except to be felt extremely ill lasted for weeks. Very rarely the patients are admitted in hospitals only in cases of spleenic rupture or for airways compromisation (Jensen 2000) [7]. In hospitals, usually the antibiotics are prescribed for the treatment of "mono" strep throat and tansilytis. An antibiotic ampicillin is not generally given to the patient as it sometimes produces maculopapular rashes on the body. But, nothing more to worry about it will go away as soon as the use of the same antibiotic is discontinued.

Burkitt's lymphoma is a kind of rapidly growing B-cell, NHL cancer mainly associated with impaired immunity has always been fatal if left untreated. Quick biopsy is required for suspected tissues of Burkitt's lymphoma. It can easily be treated within a short period of time and long term survival is achieved by chemotherapy. More than 90 % cure rate has been achieved in developed countries (Molyneux *et al.* 2012) [23]. Intrathecal chemotherapy is done when infections spread in the fluid surrounding the brain and spinal cord. Various drug combinations including vincristine, doxorubicine, cyclophosphamide, rituximab bavacizumab, prednisone, fostamatinib disodium, bortezomib, lenalidomide have been tried (Gaidarova *et al.* 2009, Reddy *et al.* 2009, Rodriguez *et al.* 2009, Friedberg *et al.* 2010 and Stopeck *et al.* 2010) [57-61]. Lastly, there is no vaccine available for the prevention of the same virus (Sharma and Rouce 2019 and Van Zyl *et al.* 2019) [62, 63].

CONCLUSION

Epstein Barr Virus is human herpes virus-4 causing a disease named infectious mononucleosis in human. This is colloquially known as the teenager's kissing disease as the disease is easily transmitted through saliva. As this is a very common virus distributed globally, it affects almost every individual of the world. As the virus has got lifelong latency in human if reactivated in future it may cause several diseases including cancer in human. Some of them are acute cerebellar ataxia, multiple sclerosis, systemic lupus erythematosus, hairy leukoplakia, malignant lymphoproliferative diseases, Hodgkin and non-Hodgkin lymphomas, B and T cell lymphomas, Burkitt's lymphoma, nasopharyngeal carcinoma, breast cancer and gastric carcinoma. Further, as the vaccines are not yet available to prevent the EBV infections or boosting immune responses against the EBV-associated tumors, the disease is still proved to be fatal for humans. The development of a suitable vaccine could have a substantial impact on reducing the burden of EBV cancer (Sharma and Rouce 2019 and Van Zyl *et al.* 2019) [62,63]. Last but not the least, as the cancer itself is not an infectious disease, the infectious agents can contribute to the origin of cancer. We should nothing more to worry about it except to be alert as cancer takes years and even decades to develop. Moreover, this is also true that not all carriers of the viruses will develop the cancer in future but certainly who develops, it is his bad luck (Masroor *et al.* 2018 & 2019 and Salim *et al.* 2019 & 2020) [64-67].

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