http://dx.doi.org/10.5272/jimab.2013194.359

ISSN: 1312-773X (Online)

Journal of IMAB - *Annual Proceeding (Scientific Papers)* 2013, vol. 19, issue 4

EPSTEIN-BARR VIRUS AND CYTOMEGALOVIRUS - TWO HERPES VIRUSES WITH ORAL MANIFESTATIONS

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SUMMARY:

Diseases caused by cytomegalovirus and Epstein-Barr virus are reported with increasing frequency. Epstein-Barr virus damages usually are due to reactivation of latent infection. While cytomegalovirus disease result from primary or reactivated infection in susceptible hosts. The booth infections can have oral manifestations.

Key words: oral cavity, cytomegalovirus, EBV

INTRODUCTION:

Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are herpesviruses, which account for the majority of oral viral infections. Herpes simplex virus, varicella-zoster virus, and Epstein-Barr virus infections nearly always result from reactivation of latent virus, while cytomegalovirus infections, besides presenting as reactivated disease, are almost as likely to present as a primary infection in susceptible hosts [1]. Herpesviruses are common in persons infected with the human immunodeficiency virus (HIV) [2]. The diseases or medical treatments that have cytostatic or cytotoxic effects also increase the risk of viral infections [1].

The general characteristic of CMV and EBV is presented in tabl. 1.

Tabl. 1. The main characteristic of EBV and CMV [1, 3, 4, 5, 6, 7]

Signs	Epstein-Barr virus	Cytomegalovirus
Herpesviruses type	HHV - 4	b-herpesvirus HHV - 5
Transmission	body fluids (saliva, breast milk, respiratory secretions) sexual contact *blood transfusion* or by sharing food, drinks or eating utensils with an infected person	body fluids (breast milk, saliva, urine, respiratory secretions) sexual contact blood transfusion during delivery organ transplant
Exposition	80 - 90% of the adult population have been infected by the virus (35-40 years)	60-70% of the adult population has been exposed
Predisposed people	It is frequently seen in individuals infected with the human immunodeficiency virus (HIV) and less often in other immunosuppressed individuals	Manifestation of CMV are more evident in immunocompromised population , such as organ transplant patients and who have AIDS
Virus targets	When the virus is dormant, it is hiding in an inactive form in B lymphocytes - "latent" state	Once exposed to CMV, this virus establishes latency within the connective tissue cells, such as the endothelium of blood vessels, mononuclear cells, white blood cells, and epithelial cells
Clinical variants	EBV can lead to: infection mononucleosis oral hairy leukoplakia plasmablastic lymphoma Burkitt lymphoma Hodgkin lymphoma nasopharyngeal carcinoma Kikuchi histocytic necrotizing lymphadenitis	Primary infection may be asymptomatic or cause an infectious mononucleosis like disease

Cytomegalovirus

Cytomegalovirus is responsible for a significant percentage of asymptomatic viral infections worldwide. During childhood, many people acquire primary infection with cytomegalovirus and if they later become immunosuppressed, such as occurs with human immunodeficiency virus (HIV), CMV is likely to become reactivated (4). For the medical doctors and dentists is important that between 11 and 24% of children attending day-care centers have CMV in their saliva [3].

Although virtually any cell or organ may be infected [8]. Severe disease caused by CMV have been reported – CMV retinitis, gastritis, colitis, pneumonia, encephalitis and hepatitis [4]. After hematopoietic stem cell transplantation cytomegalovirus is the most common cause of pneumonia within the first 120 days [3]. There is a date that CMV within endothelial cells may contribute to vascular inflammation, vascular occlusion, and end-organ damage [3].

Epstein-Barr virus

EBV infection is transmitted from person to person by contact with infectious body fluids (saliva, breast milk etc). Oral contact with infectious saliva is the most common route of transmission. The active virus reproduces and enters the person's saliva, a process known as "shedding" [7]

In EBV two peaks of infection are seen: the first in very young preschool children aged 1 - 6and the second in adolescents and young adults aged 14 - 20 [3].

In primary infection, EBV infects B cells and can cause mucocutaneous manifestations in infectious mononucleosis (IM) or acute EBV-associated syndromes such as Gianotti-Crosti syndrome and hemophagocytic syndrome [3, 5, 9].

There are two different types of chronic active Epstein-Barr virus (CAEBV) infection: chronic EBV (CEBV) having persistent infectious mononucleosis - like illness with relatively good prognosis, and severe CAEBV (SCAEBV) infection that has rather severe manifestations and generally poor prognosis (10). Latent EBV infection may result in diseases such as hydroa vacciniforme, hypersensitivity to mosquito bites, and lymphoproliferative disorders such as plasmablastic lymphoma, oral hairy leukoplakia, and post-transplant lymphoproliferative disorders, particularly in immunocompromised patients. Latent EBV infection has also been implicated in Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and Kikuchi histocytic necrotizing lymphadenitis [5, 10].

Like all herpesviruses, EBV establishes a life-long, persistent infection of its host [7] and in the majority of humans without causing disease [5]. JA Thomas, et coworkers published that in the literature are reports of EBV infection in normal T cells and neoplastic T-cell diseases. Generally EBV is held to infect B cells and epithelial cells [11].

In Table 2 are present the clinical findings of Cytomegalovirus infection and infectious mononucleosis concerning the general health. In Table 3 are present only the oral manifestation of Cytomegalovirus infection and infectious mononucleosis

Table 2. Clinical signs of Cytomegalovirus infection and infectious mononucleosis [3, 8, 12]

	Infectious mononucleosis	**Cytomegalovirus infection**
Sites most often involved	liver and spleen (splenic enlargement and tenderness and hepatomegaly)	liver and spleen (hepatosplenomegaly)
Other symptoms	significant fatigue headaches or joint pain bilateral edema of the upper eyelids (palpebral edema) nausea and vomiting, or decreased appetite jaundice skin rash blood cells (trombocytopenia) fever: adults 38.3–38.9°C; children may not have	lung (severe viral pneumonia) GI tract (colitis) central nervous system (encephalitis) blood cells (trombocytopenia) and multisystem involvement (fever of unknown origin)
Uncommon sites of infections in immunocompetent individuals include		the kidneys adrenals eye (cmv retinitis) pancreas and esophagus involvment

Oral manifestations

Table 3. Oral manifestations of CMV, EBV and particularly IM [2, 3, 4, 12, 13, 14, 15, 16, 17]

EBV	IM	CMV
• hairy leukoplakia • nasopharyngeal carcinoma • infectious mononucleosis	• sore throat (pharyngitis) • tonsillitis • petechiae on hard palate • gingivitis (necrotic ulseroza) • lymphadenopathy • salivary gland enlargement	• nonspecific oral ulcerations • periodontal disease (resembling) • carcinoma (mucoepidermoid) of major and minor salivary glands • polymicrobial infection with HS V or VZV • salivary gland enlargement

EBV

• hairy leukoplakia

Hairy leukoplakia is the second most common HIV-associated oral mucosal lesion and usually is localisated on the lateral borders of the tongue. The typical clinical appearance is vertical white folds oriented as a palisade along the borders of the tongue [3].

• nasopharyngeal carcinoma

Preliminary investigations suggest that the presence of EBV genomes in neck metastases from an occult primary may be diagnostic and predictive of nasopharyngeal carcinoma [18].

IM

In the majority of cases of IM lymphadenopathy is present and the cervical lymph nodes are most commonly involved, but generalized lymphadenopathy may occur [12]. Swelling of anterior and posterior cervical lymph nodes plus axillary, epitrochlear, mediastinal, and mesenteric nodes) or auricular adenopathy, marked adenopathy, or inguinal adenopathy are described [12].

Other manifestation of IM can be salivary gland enlargement. Several viruses have been associated with acute nonsuppurative salivary gland enlargement. The viruses responsible for the majority of virally induced salivary gland enlargement are paramyxovirus, cytomegalovirus HIV, and hepatitis C virus. Echoviruses, Epstein-Barr virus, parainfluenza virus, and choriomeningitis virus infections have been linked to occasional reports of nonsuppurative salivary gland enlargement [3].

CMV

The effects of human CMV on cellular functions which may be associated with the malignant phenotype include the expression of oncogenes and transcriptional activation of growth factors and interleukin synthesis [19].

In another study M. Melnick et coworkers discus the association of CMV and variety of malignancies, including brain, breast, lung, colon, and prostate. The authors concluded that CMV is an important component of tumorigenesis (20).

In oral cavity CMV may be present as a single large necrotic painful ulcer and less often as multiple ulcers, present for weeks or months at any site may be involved (3). Up to one-third of such ulcers are coinfected with other viruses of the herpes family, especially herpes simplex virus and varizella zoster virus (VZV) [3, 15, 21]. There have been occasional reports of mandibular osteomyelitis and tooth exfoliation associated with CMV and VZV infection [3].

Some authors reported CMV oral lesions in HIV infected patients and emphasize that CMV mucosal ulceration may be the initial manifestation of AIDS [13, 16, 17, 22].

The infection of CMV affects also the composition of the saliva: IgG, and albumin were higher in patients, but total protein were lower [23].

CONCLUSION:

The clinical manifestations of these viruses are similar and most commonly affected liver, spleen and lymph node. In the oral cavity the viral sins are unspecific and uncommon.

The dentist first can recognize the oral manifestations of the underlying disease, taking in a part that the number of immunocompromised population will get increase.

REFERENCES:

1. Schubert MM. Oral manifestations of viral infections in immunocompromised patients. *Curr Opin Dent*. 1991 Aug;1(4):384-397. [PubMed]

2. Glick M, Cleveland DB, Salkin LM, Alfaro-Miranda M, Fielding AF. Intraoral cytomegalovirus lesion and HIV-associated periodontitis in a patient with acquired immunodeficiency syndrome. *Oral Surg Oral Med Oral Pathol*. 1991 Dec;72(6):716–720. [PubMed]

3. Greenberger M, Glick M, Ship J. Transplantation medicine in: *Burket's oral medicine*. 2008, 461 -481.

4. Dodd CL, Winkler JR, Heinic GS Daniels TE, Yee K, Greenspan D. Cytomegalovirus infection presenting as acute periodontal infection in a patient infected with the human immunodeficiency virus. *J Clin Periodontol*. 1993 Apr;20(4):282-285. [PubMed]

5. Mendoza N, Diamantis M, Arora A, Bartlett B, Gewirtzman A, Tremaine

AM, et al. Mucocutaneous manifestations of Epstein-Barr virus infection. *Am J Clin Dermatol*. 2008; 9(5):295-305. [PubMed]

6. Wurapa AK, Luque AE, Menegus MA. Oral hairy leukoplakia: a manifestation of primary infection with Epstein-Barr virus? *Scand J Infect Dis*. 1999;31(5):505-506. [PubMed]

7. Walling DM. Oral Hairy Leukoplakia: An Epstein-Barr Virus-Associated Disease of Patients with HIV. *Res Initiat Treat Action*. 2000 Dec;6(4):10-5. [PubMed]

8. Jones AC, Freedman PD, Phelan JA, Baughman RA, Kerpel SM. Cytomegalovirus infections of the oral cavity. A report of six cases and review of the literature. *Oral Surg Oral Med Oral Pathol*. 1993 Jan;75(1):76-85. [PubMed]

9. Jain N, Bhatia V, Lattoo S. Epstein-Barr virus and associated head and neck manifestations. *Ann Nigerian Med*. 2011; 5:38-41. [CrossRef]

10. Song HM, Wu XY, Wang W, Xing Y, Li F, Qiu JJ, et al. Clinical characteristics and follow-up of 12 cases with severe chronic active Epstein-Barr virus infection. *Zhonghua Er Ke Za Zhi*. 2009 Sep;47(9):682-6. [PubMed]

11. Thomas JA, Cotter F, Hanby AM, Long LQ, Morgan PR, Bramble B, et al. Epstein-Barr virus-related oral T-cell lymphoma associated with human immunodeficiency virus immunosuppression. *Blood*. 1993 Jun 15;81(12): 3350-6. [PubMed]

12. Ebell MH. Epstein-Barr virus infectious mononucleosis. *Am Fam Physician*. 2004 Oct 1;70(7):1279-87. [PubMed]

13. Kanas RJ, Jensen JL, Abrams AM, Wuerker RB. Oral mucosal cytomegalovirus as a manifestation of the acquired immune deficiency syndrome. *Oral Surg Oral Med Oral Pathol*. 1987 Aug;64(2):183–189. [PubMed]

14. Epstein JB, Sherlock CH, Wolber RA. Oral manifestations of cytomegalovirus infection. *Oral Surg Oral Med Oral Pathol*. 1993 Apr;75(4):443–451. [PubMed]

15. Birek C, Patterson B, Maximiw WC, Minden MD. EBV and HSV infections in a patient who had undergone bone marrow transplantation: Oral manifestations and diagnosis by in situ nucleic acid hybridization. *Oral Surg Oral Med Oral Pathol*. 1989 Nov;68(5):612–617. [PubMed]

16. Heinic GS, Northfelt DW, Greenspan JS, MacPhail LA, Greenspan D. Concurrent oral cytomegalovirus and herpes simplex virus infection in association with HIV infection. A case report. *Oral Surg Oral Med Oral Pathol*. 1993 Apr;75(4):488-94. [PubMed]

17. Heinic GS, Greenspan D, Greenspan JS. Oral CMV lesions and the HIV infected. Early recognition can help prevent morbidity. *J Am Dent Assoc*. 1993 Feb;124(2):99-105. [PubMed]

18. Macdonald MR, Freeman JL, Hui MF, Cheung RK, Warde P, McIvor NP, et al. Role of Epstein-Barr virus in fine-needle aspirates of metastatic neck nodes in the diagnosis of nasopharyngeal carcinoma. *Head Neck*. 1995 Nov-Dec;17(6):487-93. [PubMed]

19. Cinatl J Jr, Cinatl J, Vogel JU, Rabenau H, Kornhuber B, Doerr HW. Modulatory effects of human cytomegalovirus infection on malignant properties of cancer cells. *Intervirology*. 1996;39(4):259-69. [PubMed]

20. Melnick M, Deluca KA, Sedghizadeh PP, Jaskoll T. Cytomegalovirus-induced salivary gland pathology: AREG, FGF8, TNF-6, and IL-6 signal dysregulation and neoplasia. *Exp Mol Pathol*. 2013 Apr;94(2):386-97. [PubMed] [CrossRef]

21. Regezia JA, Eversoleb LR, Barkerc BF, Rick GM, Silverman S Jr. Herpes simplex and cytomegalovirus coinfected oral ulcers in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996 Jan;81(1):55-62. [PubMed]

22. Firth NA, Rich AM, Reade PC. Oral mucosal ulceration due to cytomegalovirus associated with human immunodeficiency virus infection. Case report and brief review. *Aust Dent J*. 1994 Oct;39(5):273-5. [PubMed]

23. Marder M, Barr CE, Mandel ID. Cytomegalovirus presence and salivary composition in acquired immunodeficiency syndrome. *Oral Surg Oral Med Oral Pathol*. 1985 Oct;60(4):372-376. [PubMed]

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