

Center for Diagnostic Sciences BULLETIN



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This bulletin focuses on the role of the herpesvirus in the periradicular infection. We thank Dr. Mohammad Sabeti for his contribution to this issue. As always, we invite your comments, questions, and suggested topics for future bulletins. Please forward your comments to Ms. Latresa Lawson at llawson@usc.edu or (213) 821-2336.

What is the periradicular infection?

Periradicular (PR) lesions are infectious disorders that progress with periods of exacerbation and remission and exhibit a variety of clinical and radiographic manifestations. Limited information is available on the microbial etiology and immune responses of acute PR lesions. PR acute infections are frequently associated with black-pigmented anaerobic rods, but other anaerobic bacteria may also cause flare-up of inflammation and acute symptoms. Acute PR infection eventually turns into a chronic state predominated by macrophages, lymphocytes and plasma cells encapsulated in collagenous connective tissue. Also, chronic PR lesions develop frequently without an antecedent acute phase. Determinants of the infectious state of PR lesions are poorly understood.

What are herpesviruses?

Herpesviruses consist of a single double-stranded DNA molecule enclosed in a viral envelope. Eight human herpesviruses are currently identified: herpes simplex virus 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus-6, human herpesvirus-7 and human herpesvirus-8 (Kaposi's sarcoma virus).

The initial herpesvirus infection is followed by a latent phase in host cells that ensures survival of the viral genome throughout the lifetime of infected individuals. The alpha herpesviruses (herpes simplex and varicella zoster virus) establish latency in long-lived non-dividing neuronal cells in sensory ganglia. Human cytomegalovirus and herpesviruses-6 and -7 are beta herpesviruses, which establish latency in bone marrow-derived myeloid progenitor cells. The gamma herpesviruses Epstein-Barr virus and herpesvirus-8 are latent in B-lymphocytes.

Are there any herpesviruses in PR lesions?

cDNA identification of genes transcribed late during the infectious cycle of herpesviruses was used to indicate herpesvirus active infection in PR infection. The findings obtained revealed a strong association of human cytomegalovirus and Epstein-Barr virus with symptomatic PR lesions. PR lesions harbouring cytomegalovirus-Epstein-Barr virus dual infection tended to show elevated occurrence of anaerobic bacteria, be symptomatic and exhibit large size radiographic bone destruction.

How does transmissions of the Herpesviruses occur?

Herpesvirus transmission occurs by intimate contact with infected secretions including saliva. Acquisition of herpesviruses takes place at an early age and sometimes in the uterus. A notable exception is herpesvirus-8 that is contracted in adulthood.

How are herpesviruses reactivated?

Herpesvirus reactivation may occur spontaneously or as a result of concurrent infection, fever, drugs, tissue trauma, emotional stress and other factors impairing the host immune defense. Following activation, various herpesviruses can infect monocytes/macrophages, T- and B-lymphocytes, epithelial cells, endothelial cells, fibroblasts and other mammalian cells.

What is the hallmark of Herpes virus infection in PR lesions?

The hallmark of herpesvirus infections is immune impairment. Herpesvirus infections trigger an array of host responses that include dysregulation of macrophages and lymphocytes. Histo-pathologic features of PR pathosis are consistent with the role of herpesviruses in symptomatic PR disease. PR granulomas contain numerous macrophages and T-lymphocytes that are host cells of cytomegalovirus and which seem to be important in PR tissue destruction. B-lymphocytes are present in PR pathosis and constitute the host cells of Epstein-Barr virus. Cytotoxic CD8⁺ T-lymphocytes, which constitute the key element of the anti-herpesviral host defense, can occur in high numbers in PR pathosis. PR granulomas also contain natural killer (NK)-cells, which are populations of large lymphocytes that accumulate at sites of viral replication and contribute to protective responses against herpesvirus infections through mechanisms of cytotoxicity and cytokine production without prior sensitization.

Herpesviruses interfere with innate and adaptive cellular and humoral immune effector mechanisms by affecting cytokine networks, activation and silencing of NK-cells, down-modulating antigen presentation in the major histocompatibility complex (MHC) class I and II pathways, and regulating apoptosis. Cytomegalovirus infection gives rise to a typically pro-inflammatory cytokine profile, with production of interleukin (IL)-1 β , IL-6, IL-12, tumor necrosis factor (TNF)- α , interferon (IFN)- α/β , and IFN- γ .

Cytokines and chemokines produced in Epstein-Barr virus infection includes IL-1 β , IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, IL-18, TNF- α , IFN- α/β , IFN- γ , monokine induced by IFN- γ (MIG), IFN- γ -inducible protein 10 (IP-10) and granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF tends to occur at elevated levels in symptomatic and large size PR lesions. Several of the herpesvirus-associated cytokines have been identified in PR lesions where they may exert bone resorption potential.

How are Herpesviruses associated with periradicular pathosis?

Our proposed etio-pathogenic model of herpesvirus-bacteria-host responses explains development of PR pathosis. Initially, bacterial infection or mechanical trauma of the pulp cause herpesvirus-infected inflammatory cells to enter pulpal tissue through the PR region. Subsequent herpesvirus reactivation gives rise to enhanced inflammatory mediator and cytokine responses in macrophages and other host cells. Lipopolysaccharide from resident gram-negative bacteria can also stimulate cytokine responses in inflammatory cells. Triggering of pro-inflammatory cytokines may induce PR bone resorption or, in a vicious cycle, reactivate latent herpesviral infections. Diminished resistance of pulpal and PR tissue may also lead to overgrowth of pathogenic bacteria or possibly cytotoxicity and tissue necrosis.

What about the variety of clinical and radiographic manifestations of PR infection?

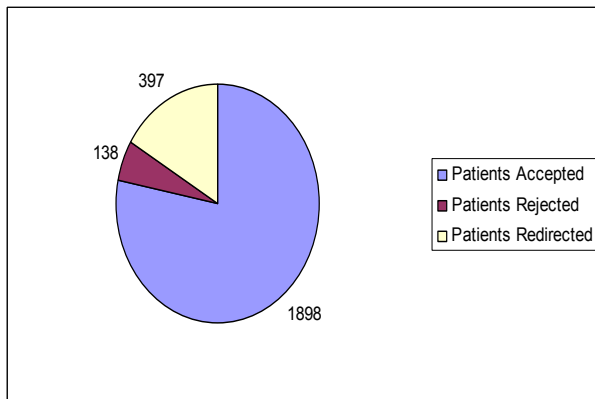
Herpesviral-bacterial interactions may help explain alteration between prolonged periods of herpesvirus latency interrupted by periods of activation and may be partly responsible for intermittent episodes of PR disease flare-up. Frequent reactivation of PR herpesviruses in some patients may result in rapid disease progression. Perhaps not coincidentally, herpesvirus-activating factors are also risk factors for acute endodontic disease. Absence of herpesviral infection or reactivation and lack of endodontic pathogenic bacteria may explain why some teeth having a necrotic pulp can maintain PR health or minimal disease for extended periods of time.

What is the significance of these findings?

Studies on herpesviral-bacterial interactions in endodontic pathosis may hold great promise for delineating important etiologic and pathogenic aspects of PR pathosis. If the etio-pathogenesis of PR lesions indeed includes herpesvirus-mediated tissue destruction, a new direction to prevent and treat apical periodontitis may focus on controlling the causative viruses. Also, future vaccination against herpesviruses might help diminish the severity of PR pathosis.

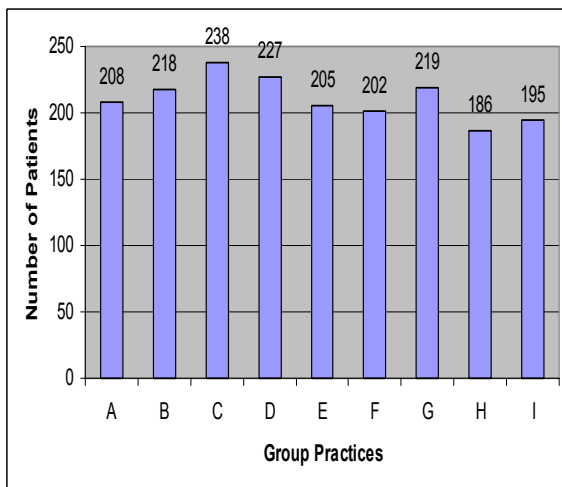
Did you know?

Number of patients accepted, rejected, & referred between September 29, 2003 to April 29, 2004



Total Patients seen = 2433

Number of patients assigned to each group practice



Average number of accepted patients per session

