Human cytomegalovirus-associated oral and maxillo-facial disease
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ABSTRACT
Human cytomegalovirus is a ubiquitous pathogen with protean clinical manifestations. After initial infection, the virus remains in a persistent state in the host. Immunity plays a pivotal role in counteracting its virulence, albeit intermittent virus shedding occurs in immunocompetent individuals. Should deficiencies in immunity occur, e.g., as a consequence of AIDS or iatrogenic immunosuppression, then virus replication and subsequent pathogenic manifestations ensue. In the oral and maxillofacial region, the virus causes a wide variety of diseases, mainly atypical chronic ulcerations and sialadenitis. These morbidities are rarely reported and sometimes cause significant problems for clinicians.

Keywords AIDS, atypical ulceration, cytomegalovirus, immunosuppression, sialadenitis, transplantation


Human cytomegalovirus (HCMV) is an omnipresent pathogen, with a seroprevalence among adults of 50–100%. Seropositivity against HCMV reaches 50–80% in heterosexual individuals who are seronegative for human immunodeficiency virus (HIV), whereas homosexual HIV-seropositive males are almost always seropositive for HCMV [1]. Seroconversion is also prominent among individuals with poor socio-economic status and/or in developing countries [2]. Body fluids or bone marrow/solid grafts are the means of HCMV transmission. The primary infection is usually of no clinical importance, unless it involves a neonate or an immunosuppressed individual [3]. Given that the host immune system cannot eliminate HCMV, a persistent latent infection follows. Although the virus is mainly harboured by cells of myeloid lineage, HCMV can promiscuously affect several different cell types [4]. During latency, viral protein synthesis is repressed in an effort to evade the immune system, although some virus ‘leakage’ can be detected. Consequently, equilibrium is established between the virus and the host. Should the host become stressed, virus reactivation and shedding ensue [4].

In terms of pathology, HCMV is a major pathogen that causes infections of neonates [4]. It also complicates organ allografts (especially cardiac transplantation) and immunosuppressive post-transplant therapy, and potentially causes serious morbidity or mortality in patients receiving chemotherapy for cancer or collagen disease, or in individuals suffering from AIDS, particularly if at an advanced stage [2,5,6]. It also plays a pivotal role in atherosclerosis formation and restenosis following coronary angioplasty [3]. HCMV is also responsible for a variety of other diseases, ranging from an asymptomatic, sub-clinical infection to an infectious mononucleosis (in contrast to Epstein–Barr virus, HCMV rarely causes tonsillo-pharyngitis or splenomegaly) in otherwise healthy individuals [4]. In the context of oral and maxillo-facial pathology, HCMV causes mainly persistent, atypical oral mucosal ulcers and major salivary gland infections, with or without concomitant alterations in salivary flow, which are mainly secondary to profound immunosuppression [6,7]. Rare and diverse manifestations of HCMV infection, e.g., gingival...
hyperplasia, gingivitis, periodontitis, osteomyelitis of the jaw, sinusitis, hyperplasia of the oral mucosa, and concurrent infection in Kaposis sarcoma and recurrent aphthous stomatitis, have also been reported [2,7–9]. Oral ulcerations (attributed to HCMV, individually or synergically with other herpes viruses, Histoplasma capsulatum, or even mycobacteria) occur predominantly in conjunction with immunosuppression [10–12]. Such ulcerations show diversity in terms of clinical appearance, duration (range 12–21 weeks) and localisation. Any oropharyngeal site can be involved, but ulcerations of the hard–soft palate are the most prevalent [1,2,5]. Such lesions usually present as long-lasting, solitary or numerous, painful or painless, medium-sized, shallow ulcerations. Their base can be covered by a yellow slough or pseudomembrane, and the margins can be rolled, elevated, with induration or devoid of induration [1,2,5,7,10]. Cervical lymphadenitis and pyrexia are seen inconsistently. Therefore, HCMV-associated ulcerations are non-specific, and the differential diagnosis includes various nosological entities [11]. Indeed, in some cases, the clinical appearance is misleading, resulting in treatment failure and a resulting biopsy [8].

Pathogenetically, endothelial infection is allegedly the instigating factor for the development of epithelial ulceration (as found in similar cutaneous and gastrointestinal lesions), unless other infectious agents with epithelial tropism are identified. It seems that small blood vessels are obstructed, rendering the tissue ischaemic so that an ulcer ensues [2,7]. In addition, HCMV can cause parotitis in neonates. The virus remains active during the first year of life in 15–50% of infants, but then remains in a dormant state in salivary gland cells [6]. During this period, HCMV parotitis could be a cause of sudden infant death syndrome, since the immune system is under-developed, as indicated by post-mortem studies conducted in children [13]. However, these findings are contentious, since a massive virus reactivation is known to occur upon death (J. Sinclair, personal communication).

In adults, local virus reactivation usually presents in the form of sialadenitis or symptoms of salivary dysfunction following immunosuppression [6]. In this context, Greenberg et al. [6] found that local HCMV reactivation is responsible for xerostomia, with or without the salivary enlargement encountered in AIDS patients, affecting primarily sub-mandibular and sub-lingual or parotid glands. In such cases, the degree of HCMV-induced sialadenitis and/or xerostomia was commensurate with the HIV load, and was inversely proportional to the CD4+ cell count. In cases where the CD4 count was >220 cells/mm³, salivary enlargement was attributed to lymphocyte infiltration in the salivary parenchyma. Such tumefaction could even mimic a tumour [6,14]. Overall, it can be concluded that HCMV causes protein clinical manifestations, albeit infrequently, in the oral and maxillo-facial region, ranging from non-specific ulceration and salivary enlargement, to lesions such as periodontitis and sinusitis.

Epidemiologically, HCMV oral and maxillo-facial infections have increased dramatically during the last three decades. Almost all HCMV oral and maxillo-facial infections now occur in patients with chronic HIV infection, with a handful of cases involving transplantations, malignancy and immunosuppressive treatment (in most of these cases, the CD4 count was <100 cells/mm³) [2,5,6]. With HIV-infected patients, particularly when the CD4 count is <100 cells/mm³, HCMV reactivation takes place. HIV patients harbour multiple HCMV strains, and compartmentalisation of these strains occurs [15]. Such strain mixtures, along with recombination events and viral polymorphism, confer evolutionary advantages in terms of virulence, drug resistance and tropism [15]. HCMV also promotes HIV provirus activation, or HIV tropism, through the expression of glycoprotein U528 (which mimics the CXCR4 and CCR5 chemokine receptors), cytokine release, and up-regulation of the CD4 receptor when both viruses coexist in the same or bystander cells [16].

In terms of aetiopathogenesis, HCMV lesions generally result from reactivation of a latent virus or re-infection by another strain (or recombination), and, less frequently, from a primary infection. Several different scenarios are possible with respect to the source of the virus. First, endothelium and ductal or mucosal epithelia could host latent HCMV, with immunosuppression resulting in its reactivation; indeed, periodontal tissues have recently been implicated as the source of HCMV salivary shedding in patients with periodontitis [17]. Second, HCMV could colonise endothelial cells during the course of a blood-borne infection, since detection of HCMV may occur in parallel with viraemia; moreover, in the
event of disseminated HCMV disease, virus spread is facilitated by means of detached endothelial cells from remote infected sites or engagement-tethering of infected peripheral blood cells to endothelium, through an intercellular adhesion molecule-1 (endothelial cell) and a leukocyte function-associated molecule-1 (polymorphonuclear leukocyte) or membrane-activated complex-1 (monocyte) interaction [18]. In addition, HCMV induces a monocyte-to-macrophage differentiation, thus facilitating virus dissemination from blood to peripheral tissues [19]. Third, the presence of HCMV could result from auto-inoculation by the shedding of HCMV through saliva (or even semen) [20]. Finally, dendritic cells could form a true reservoir of virus [21] (J. Sinclair, personal communication).

REFERENCES