

# ORAL MANIFESTATIONS OF THE HUMAN HERPESVIRUSES

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## REZUMAT

Manifestările orale ale virusurilor herpetice pot fi observate de o serie de specialiști, cum ar fi pediatri, medici de familie, dentiști etc. Leziunile virale pot fi întâlnite îndeosebi la indivizii imuno-deprimati, al căror număr este în creștere în practica curentă. În condițiile în care mucoasa orală este zona pe care pot fi observate manifestările virusurilor, este importantă cunoașterea, ca și tratamentul acestora.

**Cuvinte cheie:** virus herpetic, mucoasă orală, manifestări orale

## ABSTRACT

Oral herpetic viruses manifestations can be noticed by many medicine professionals, as pediatricians, general practitioners, dentists etc. Viral lesions can be seen especially in immunosuppressed persons, with number increase in the clinical practice. Since the oral mucosa is one of the place where this manifestations are observed, it would be useful to know the clinical pattern and their general management.

**Key Words:** herpesvirus, oral mucosa, oral manifestation

## INTRODUCTION

Oral viral manifestations in humans are often seen in the clinical practice. They can be noticed by pediatricians, general practitioners, oral surgeons, and dentists etc. Viral lesions can be seen both in healthy or diseased people. Viral manifestations appear especially in immunosuppressed persons. It is to expect that such cases be more often encountered due to various type of immunodeficiencies, which are more and more observed in the clinical practice. The oral cavity is one of the place where these manifestations are first noticed. Thus, it would be useful to describe some of types of viral lesions that have a great likelihood to be encountered in the future by many specialists.

Generally, three main viral reactions are present: cytopathic effects, latent viral infection and oncogenic effects. The viral infectious pathology of the oral

mucosa includes several diseases, heterogeneous as clinical expression, most of them recognizing as etiology the viruses from the Herpesviridae family.<sup>1</sup> From the eight known types of herpetic viruses, only six produce oral manifestations: herpes simplex type 1 and 2, Varicella-Zoster virus (human herpes type 3), Epstein-Barr virus (human herpes type 4), Cytomegalovirus (human herpes type 5) and the virus associated with Kaposi sarcoma (human herpes type 8).<sup>2,3</sup>

The manifestations on the oral mucosa are influenced by the particular characteristics of each infectious agent. Thus, the alpha-type herpetic viruses (Simplex 1 and 2, Varicella-Zoster virus), with high speed of replication and affinity for epithelial cells, produce acute inflammatory conditions on the oral mucosa. The gamma-type herpes viruses (Epstein-Barr virus and HHV8), with low speed of replication and affinity for lymphocytes, induce cell proliferation, sometimes with malignant characteristics.<sup>1</sup>

## THE ORAL MANIFESTATIONS OF THE INFECTION WITH HERPES SIMPLEX (TYPE 1 AND 2)

The infections with herpes viruses type 1 and 2 produce quite similar clinical manifestations on the oral mucosa: the primary herpetic gingivostomatitis and the recurrent secondary gingivostomatitis .

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### The primary herpetic gingivostomatitis

The primary herpes simplex type 1 infection affects in more than 85% cases the oral cavity, as an ulcerative acute gingivostomatitis.<sup>4,5</sup> (Fig. 1) The primary infection appear commonly in childhood, rarely on young adults, and it is largely oligosymptomatic.<sup>6</sup> When the infection is present in newborn children, the evolution could be severe, and can produce sometimes important complications, especially when the causal agent is Herpes simplex type 2.<sup>7</sup> The onset begins after a incubation period of 3-7 days, with a couple of prodromal signs with variable intensity, as tingling or burning sensation, followed by the typical eruption on the oral mucosa; it is formed by liquid containing vesicles, arranged "in bouquet", that lead to superficial ulcerations.<sup>8</sup>



**Figure 1.** Primary herpetic gingivostomatitis.

Unlike the aphtae, the herpetic eruption can be encountered everywhere on the oral mucosa, mainly on the attached gingiva and on the vermillion border.<sup>9</sup> Sometimes the hypertrophic inflammatory gingivitis can be seen. (Fig. 2)



**Figure 2.** Herpetic lesions on the gingiva and lower lip.

Frequently, the oral eruption is accompanied by general nonspecific signs as fever, malaise and regional lymphadenopathy, sore throat.<sup>10</sup> Sometimes, the

eruption presents acute characteristics, with multiple lesions disposed on large areas of the oral mucosa.<sup>11</sup> (Fig. 3)



**Figure 3.** Acute gingivostomatitis.

The most common complications of the primary herpetic gingivostomatitis are the bacterial supra-infection of the ulcers and the autoinoculation lesions, as the herpetic panaritium or the herpetic keratitis.<sup>2</sup> In children dehydration and very rarely herpetic encephalitis can be encountered. The clinical lesions may last from 10 to 14 days, and the healing leaves no scars.<sup>1,2</sup> The differential diagnosis must includes the secondary infection (limited eruption located only on attached gingiva and the lack of general signs and symptoms) and other ulcerative conditions as: acute necrotizing ulcerative gingivostomatitis (punched-out interdental papillae, necrotic ulcers), herpangina (ulcerations occur only on the tonsillae, soft palate and oropharynx mucosa), Zona Zoster (the rash located on a sensitive nerve trajectories) or erythema multiforme (bigger ulcers, with hemoragic aspect, simetric located on the mobile mucosa, in anterior areas of the mouth, lips, tongue) or aphtae.<sup>12</sup>

### The secondary herpetic gingivostomatitis

Oral recurrent episodes occur in only a third part of the subjects that suffered a primary infection. Several conditions may precipitate a recurrence: dental treatments, emotional stress, premenstrual syndrome, sun-light exposure.<sup>13</sup> The clinical evolution is much less severe than the primary gingivostomatitis, without fever or adenopathy.<sup>14</sup> The eruption is limited to a group of vesicles that breaks rapidly, disposed only on the attached gingiva or on the lips and surrounding skin.<sup>2</sup> (Fig. 4).

Sometimes, the secondary infection can simulate a primary milder herpetic gingivostomatitis, with less extensive lesions (Fig. 5). In immunocompetent persons, the natural tendency is of reducing the number of recurrences.<sup>15</sup> On immunodepressed

subjects, recurrences occur much frequently, especially when the lymphocyte number becomes lower than 200 units/mm<sup>3</sup>.<sup>16</sup>

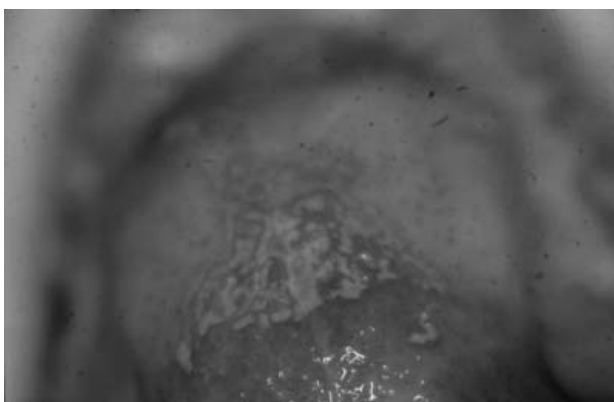


**Figure 4.** Vesicles disposed "in bouquet".



**Figure 5.** Atypical secondary herpes simplex infection.

The eruption is acute, with large, extensive ulcerative lesions, with atypical location, including the mobile oral mucosa and it last over one month duration.<sup>16</sup> (Fig. 6) These lesions are difficult to heal and are suggestive for a immunodeficiency condition on a person previously undiagnosed.<sup>16</sup>



**Figure 6.** Secondary herpetic infection on HIV positive patient (H. Szpirglas collection).

Even if the role of the Herpes simplex type 2

in oncogenesis is well known, there are not enough data to sustain a similar contribution of the Herpes simplex type 1, although numerous studies revealed the apparition of cromosomal anomalies in oral mucosa infected tissues.<sup>17</sup> Some authors claimed the possibility of the Herpes simplex type 1 role in malignisation, in association with smoking.<sup>18</sup>

The differential diagnosis of the secondary herpetic gingivostomatitis include the primary infection and other ulcerative diseases: Zona-zoster, erythema multiforme, aphtae, trauma, bulous toxicodermatosis, pemphigus (multiple chronic ulcers preceded by bullae, positive Nikolsky's Sign).<sup>1,2</sup>

The current treatment of the Herpes simplex infections of the mouth consists of nucleosidic analogs (Acyclovir®). Orientative doses are: 200mg, 5 times on day for 10 days in the primary gingivostomatitis, and for 5 days in recurrences. For children older than two years, the recommended dosis is of 80mg/kg.<sup>19</sup>

Acyclovir® can be administrated locally as ointment (5%), 3-4 times daily for a week. In resistant forms, especially on immunodepresed patients, it is indicated to use pyrophosphat analogs (Foscarnet®) iv.<sup>19</sup> Attempts to obtain a vaccine failed to-date.

### **THE ORAL MANIFESTATIONS OF THE INFECTION WITH VARICELLA-ZOSTER VIRUS**

The primary infection with the Varicella-Zoster virus occurs commonly in children as Varicella. The main clinical manifestation is the cutaneous typical rash, with elementary lesions different as age and type (maculae, papules, vesicles, pustulae, crusting), extending from the head to the trunk.<sup>20</sup> On the oral mucosa, the infection is limited at several (3-5) vesicles disposed on a erythemathous area, more frequently on the posterior aspect of the oral cavity. (Fig. 7)

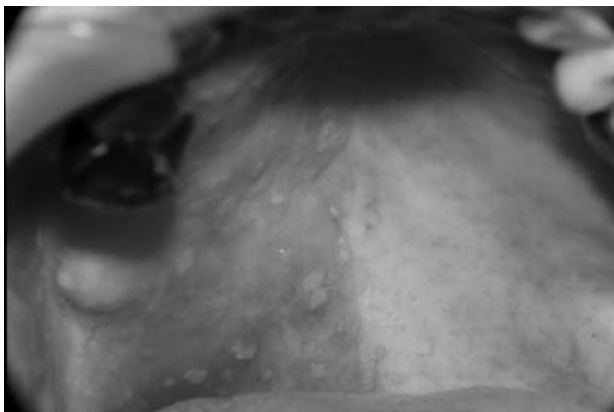


**Figure 7.** Varicella lessions on the oral mucosa.

The evolution is favourable, with the remission in 7-10 days.<sup>21</sup> In adults and immunodepressed patients, the eruption is more widespread, on several nervous branches and the lethal risk is higher.<sup>22</sup>

The recurrent infection is represented by the Zona-Zoster. The characteristic pattern of the disease is the vesicular eruption, localized strictly on a sensitive nerve trajectory. The most common affected branch of trigeminal nerve is n. ophthalmicus.<sup>1</sup> The apparition of oral mucosa lesions is preceded by prodromas as odontalgias or burning sensation. The eruption consists of painful vesicles, unilaterally disposed.<sup>23</sup> (Fig. 8)

Complications occur commonly in elder people and immunodepressed subjects, being represented by postherpetic trigeminal neuralgia, dental pulp necrosis, dental radicular resorbtion or osteonecrosis.<sup>24,25</sup> Sometimes, the lesions can be extended on the whole territory of the trigeminal nerve distribution, with severe disturbances. (Fig. 9)



**Figure 8.** Zona-zoster ulcers disposed on the great palatine nerve territory.



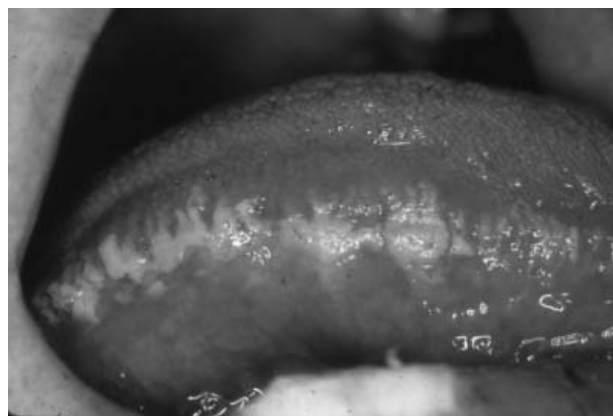
**Figure 9.** Facial Zona-zoster with extended lesions.

The treatment must be administrated early, to limit the pain, reducing the risk of postherpetic trigeminal neuralgia. The recommended therapy must include second generation antivirals as Valacyclovir<sup>®</sup> or Famcyclovir<sup>®</sup>. In old persons, a short-time and moderate dose of corticoid can be used.<sup>23</sup>

## **THE ORAL MANIFESTATIONS OF THE INFECTION WITH EPSTEIN-BARR VIRUS**

The Epstein-Barr virus has two main targets: the epithelial cells and the B-cells. The natural reservoir of the virus is the B-cells, where it can be latent and survive indefinitely. The virus produces a general acute disease, the infectious mononucleosis, which occurs mainly in young adults. The onset follows after a 3-4 weeks incubation and consists in a accute pharyngotonsilitis, associated with hepatosplenomegaly and generalized adenopathy. On the oral mucosa, the infection produces petechiae caused by thrombocytopenia and ulcers, localized at the hard and soft palate limit.<sup>26</sup> The evolution of the illness, rare severe complications as splenic rupture being possible.<sup>26</sup>

In patients with acquired immunodepression (HIV infection) or immunosuppression (lymphoma, immunosuppressor medications), the Epstein-Barr virus produces hairy leukoplakia.<sup>27,28</sup> Hairy leukoplakia may incidentally occur in immunocompetent patients [29]. The incidence of Epstein-Barr co-infection in HIV infection is higher when the CD4+ T cells count is lower than 200 units on mm<sup>3</sup>.<sup>27</sup> Hairy leukoplakia is usually asymptomatic, with linear keratotic striae disposed paralely, in plaque, on the borders of tongue. (Fig. 10) The pathology shows that the epithelium is akantothic and hiperkeratotic, with variable rough surfaces. Most cases present various regions of vacuolated keratynocytes, that can be seen in the upper spinous layer. Unlike other types of leukoplakia, no inflammatory infiltrate can be observed in the chorion. The differential diagnosis includes other keratotic lesions: oral lichen planus, trauma, idiopathic leukoplakia, oral carcinoma, allergy on dental restorative materials, other viral infections (HPV) or genetic keratotic conditions (white sponge naevus).<sup>26</sup>



**Figure 10.** Hairy leukoplakia (H. Szpirglas collection).

The Epstein-Barr virus presents affinity for the B lymphocytes and a proliferation stimulative effect. That capacity is low in immunocompetent persons.<sup>30</sup> Responsible for the proliferative effect are two viral proteins: LMP-1 (latent membrane protein) and EBNA-2 (EBV nuclear antigen). The activity of these molecules is higher when conditions of immune modulation failure appear.<sup>31</sup> The nature of the failure is strongly linked with the presence of the Epstein-Barr virus. Thus, if in the acquired immunodeficiency the incidence of virus infection is aprox. 50% of cases, in the chemical immunosuppression the incidence it is almost 100%.<sup>32</sup> On the other side, the incidence of Epstein-Barr virus co-infection in HIV infection is variable with the level of immunodepression. Since the co-infection is lower in the early HIV-infection and much higher in the AIDS, it is possible that the Epstein-Barr virus could play a key-role in the severe levels of immunodepression and just as co-factor in the moderate ones.<sup>31</sup> The Epstein-Barr virus infection is associated with the non-Hodgkin lymphoma of the oral mucosa, which develops from the lymphocytic infiltrate in the chorion or in the lymph vessels.<sup>31,32</sup> The main symptom of the lymphoma is the enlargement of the lymph nodes, spleen and liver. The laboratory investigations shows normocytic anemia, eosinophilia and important lymphopeny.<sup>31</sup> In the oral mucosa, the lymphoma typically starts as a persisting ulcerating ulceration, which subsequently develops in a tumoral mass. The most common sites of involvement are the alveolar process and the hard palate next to the soft palate. (Fig. 11) The treatment of the oral mucosa lymphomas is multimodal. Unfortunately, the response to chemotherapeutics is bad and the drug resistance appears early, by the expression of surface antigens like B cell lymphocyte type 2 (BCL-2), with powerful anti-apoptotic effect.<sup>20,31</sup>

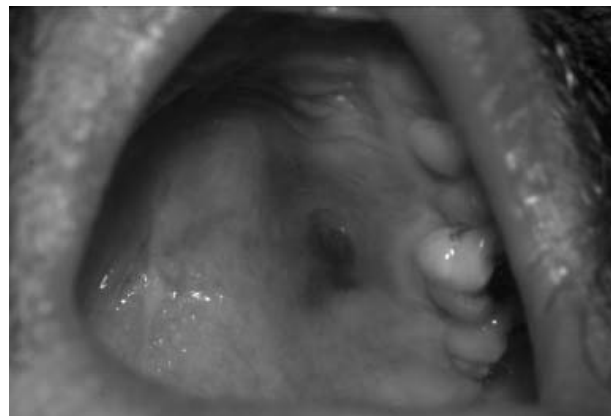


**Figure 11.** Non-Hodgkin's lymphoma located on the alveolar processus.

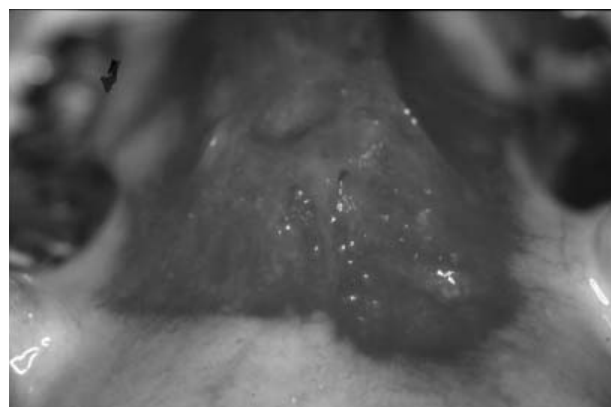
## **THE ORAL MANIFESTATIONS OF THE INFECTION WITH HUMAN HERPES 8 VIRUS**

The HHV-8 has been implicated as a causative agent in Kaposi's sarcoma and Plasmablastic lymphoma.<sup>33,34</sup>

In healthy people, Kaposi's sarcoma is a rare low malignant cutaneous tumor. It appears mostly on elderly, on the distal portion of the lower extremities, as bluish-red maculae, with slow progression. The oral Kaposi's sarcoma is a known AIDS-related malignancy, but it was observed in the immunosuppressed patients treatments too.<sup>35</sup> The disease is characterized by the abnormally growing blood vessels, in a spindle-cell mass, suggestive for angiofibrosarcoma.<sup>34</sup> The lesions are red-purple maculae, that progress into nodules or plaque, usually painless, sometimes painful and swollen. (Fig. 12) Sometimes they become large, exofitic tumors. They appear on the hard palate and much rarely on the gingiva, tongue or oropharynx.<sup>36</sup> (Fig. 13)



**Figure 12.** Kaposi's sarcoma located on the hard palate.



**Figure 13.** Kaposi's sarcoma located on ventral aspect of the tongue.

The evolution is slow, with a low rate of metastasis and frequent recurrences after the surgical excission.<sup>36</sup> In the AIDS-associated Kaposi's sarcoma, the highly active antiretroviral therapy (HAART) is the main

treatment, the incidence of Kaposi's sarcoma in HIV infection decreasing visibly in the last 10 years, since the introduction of the HAART.<sup>36</sup> The lesion must be distinguished from the amalgam tattoos, trauma and other tumors (lymphoma, angioma, malignant melanoma).

The Plasmablastic lymphoma is a particular form of non-Hodgkin's lymphoma of the oral mucosa, almost exclusively seen on HIV positive patients.<sup>37</sup> The clinical course of that disease is quite similar with the rapidly progressive B-cell lymphomas.<sup>38</sup> Morphologically, the plasmablastic lymphoma looks like the large cells lymphomas, but were CD20 and CD45-negative and expressed plasma cell-related antigens such as CD138.<sup>39-41</sup>

### **THE ORAL MANIFESTATIONS OF THE INFECTION WITH CYTOMEGALOVIRUS**

The primary infection with Cytomegalovirus is commonly asymptomatic, only in newborns existing the risk of developing some severe complications as dental hypoplasia and sensitive or motor nerve disorders.<sup>42</sup> In immunodepressed subjects, the primary infection clinical pattern is similar to the infectious mononucleosis, although the lymphadenopathy is less important.<sup>43</sup>



**Figure 14.** Cytomegalovirus ulcer.

The secondary infection occurs only in immune suppression conditions and in the acquired depression.<sup>44,45</sup> Some studies claim the possibility of the presence of HHV-8 in the Kaposi's sarcoma lesions, but the importance of that association is unclear.<sup>46</sup> The lesions on the oral mucosa are crenelated ulcers, disposed on the lips, hard palate and vestibular mucosa.<sup>45</sup> (Fig. 14) Treatment's target is the cause of the immunodepression.

### **CONCLUSIONS**

- The herpes viruses, even being of the same biologic family, induce very variable clinical manifestations on the oral mucosa.
- These appear as a result of the complex viral actions: citopathic effect, viral infection latency, oncogenesis effect.
- Some viral types (simplex and Varicella-Zoster) remain permanently harbored on the sensitive nerves nodes and produce recurrences or acute nonspecific infections, mainly on immunodepressed patients.
- Other types (Epstein-Barr, HHV8) could represent risk factors for malignant transformation.
- We can estimate that in the future, as the immunosuppressive treatments tend to expand, the herpetic viral manifestations will be more present in the pathology.
- Moreover, the oral mucosa is frequently the first site where the infections could be observed, suspecting thus a failure in the immune status of the patient. Therefore many medical professional must become familiar with such lesions, in order to detect an early immunosuppression or to manage the complications of these manifestations.

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