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Original Research Article

Non-Tumor Oral Manifestations of Viral Infections: A Systematic Review

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Abstract: The complexity of the occurrence of these oral mucosal infections highlights the need to combine an antiviral drug, in addition to the local treatment administered, in the management of oral diseases associated with viral infections. However, a careful and well-conducted clinical examination gives a good diagnostic orientation to better adapt the best therapeutic procedure. The objective of this study was to review the non-tumoral oral manifestations of viral infections through a review.

Keywords: Viral infections, oral manifestations, systematic review.

INTRODUCTION

The oral cavity is the site of expression of several general diseases, including infectious diseases [1]. Indeed, oral manifestations may be the only, the first expression or part of the clinical manifestations of viral infections [2].

These viral infections may be associated with primary lesions causing alterations of the mucosa or alter the human system of the patient, thus exposing him to develop oral pathologies [3].

The clinical forms of these oral manifestations are diverse and varied, ranging from a simple variation in the color of the oral mucosa to a malignant tumor lesion, which can be life threatening [3]. Indeed, in addition to oral mucosal lesions, these oral manifestations may go unnoticed as is the case in the covid19 pandemic where agueusia associated with anosmia are symptoms more reported in asymptomatic SARS-COV-2 virus carrier patients [4-8].

Early diagnosis will allow prompt management to avoid late complications that may alter the quality of life of patients. Hence the need to review the literature on the non-tumoral oral manifestations of viral infections in order to facilitate their detection and early diagnosis by oral health professionals.

MATERIALS AND METHODS

- The research questions that justified this review of the literature were can oral manifestations be signs of call for an early diagnosis of viral diseases?
- What are the oral manifestations most frequently encountered in viral infections?
- These questions motivated the interrogation of a number of search engines.

Inclusion Criteria

Filters such as human studies conducted between 1991 and 2021 were used in the search strategy.

The variables used for article selection were: the presence of oral events, availability of abstract and/or pdf, publication in English or French, a descriptive study, an analytical study.

Criteria for non-inclusion

Articles dealing with the subject for which the abstracts and/or pdf could not be made available. But also articles dealing with the subject published in languages other than English and French.

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Articles dealing with oral manifestations of antiviral drugs were also not included in this study.

Search Strategy

A search strategy covering the years 2011 to 2021 was adopted. PubMed, Google Scholar databases using several keywords were: viral infections, oral manifestations ("viral infections" and "oral manifestations") but also MeSH ("oral manifestation of viral disease", "oral manifestations of viral infections", "virus diseases and oral manifestations", "viral infections" to "oral manifestations"). The electronic search was complemented by a manual search.

Article selection procedures

Article abstracts from both the electronic and manual searches were reviewed. Articles that were not explicit for inclusion were discarded. Articles relevant to the research questions were retained and their full texts (pdf) downloaded for further reading. Full-text copies of articles for which the title and abstracts were not sufficiently informative for final inclusion in the journal were sought.

RESULTS

Selection of articles

The search strategy resulted in the selection of 70 articles out of a total of 1776 titles consulted at the beginning of the search (Fig 1).

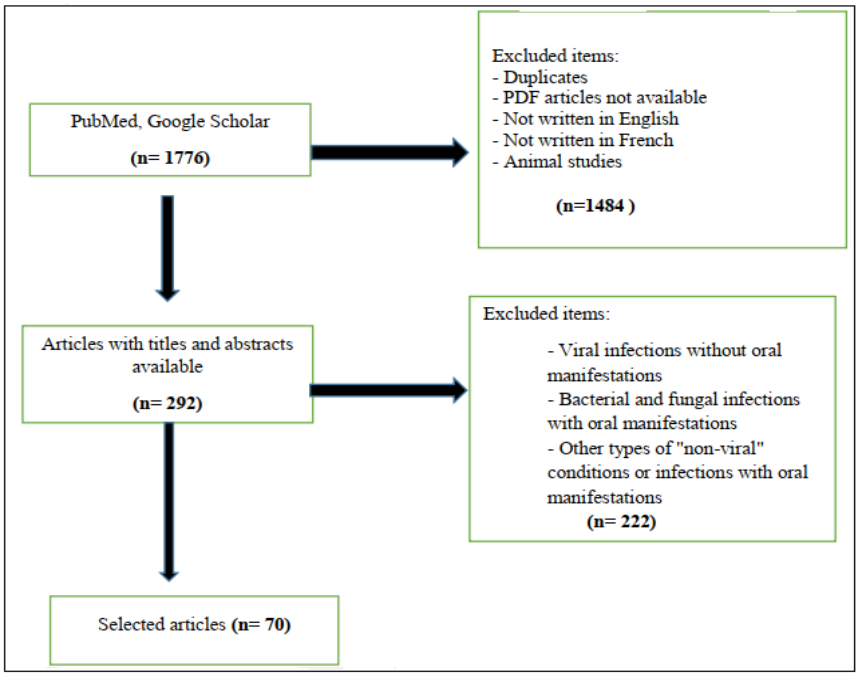


Fig 1: Flowchart Diagram

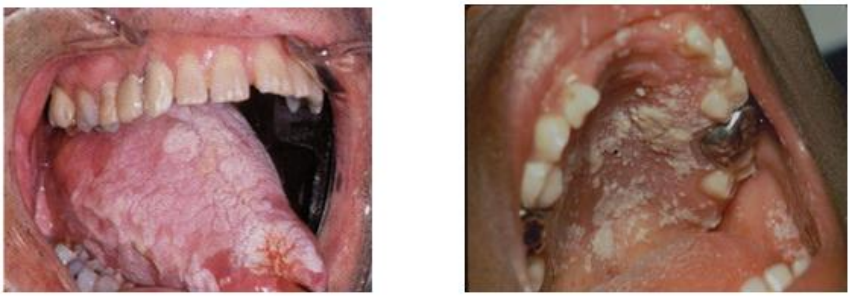
Summary of data

Loss of substances

Substance losses are represented by erosions and ulcerations (Fig 2) (Table I).

Table I: Loss of substances

Types of lesions	Types of viruses	Most frequent locations	References
Erosion	HSV-1 HSV-2 VZV Parvovirus B19 HIV SARS-CoV-2	Gum Lips Tongue Cheeks	2,6,9, 10, 11, 12, 13,14, 15, 16, 17,18, 19,20, , 21, 22,23, 24, 25, 26,**27,**28, 29, 30,31,32
Ulceration	HSV-2 CMV EBV Enterovirus HIV SARS-CoV-2 HHV-6 and HHV-7	Lips Tongue Cheeks Gum Pharynx Palate Veil Tonsils Palatal vault Luette	2, 6,9, 10, 12, 13, 14,15, 16, 19, 20,21, 22,23, 24, 25, 26,**27,** 28, 29,30, 32,34, 35,36, 37, 38



A B

Fig 2: Hyperplastic candidiasis of the tongue (A) and pseudomembranous candidiasis of the palate region (B) during HIV infection [1]

Vesicular lesions

Vesicular lesions were represented by vesicles and bullae (Table II).

Table II: Vesicular lesions

Types of lesions	Types of viruses	Most frequent locations	References
Vesicular	HSV-1 HSV-2 VZV Enterovirus SARS-CoV-2	Gum Lips Tongue Cheeks Palatal Vault Palate Veil Pharynx Tonsils	9, 12, 14,15, 17,18, 19, 20, 22, 23,24, 25, 26, **27, 30, 32,39**
Bullae	HVS-1 HVS-2 SARS-CoV-2	Tongue Cheeks Gum Palatal vault Palate Veil Lips	2, 6,9, 13,14, 17, 19, 20, 21, 22,23, 24, 26, 29, 30, 32, 39,

Leukoplakic lesions

Leukoplakic lesions were represented by oral hairy leukoplakia, cheilitis and candidiasis (fig 3) (Table III).

Table III: Leukoplakic lesions

Types of lesions	Types of viruses	Most frequent locations	References
Oral Hairy Leukoplakia	HIV Hepatic viruses SARS-CoV-2 EBV	Tongue	2,9, 10, 12, 13,14, 29, 52, 68, 25, 31, 33, 37, 39, 30, 35
Cheilitis or Perlchea	Parvovidae HIV SARS-CoV-2	Lips	10, 12, 13, 14, 24, 22,23, 32, 39, 30, 35
Candidiasis	HIV SARS-CoV-2	Tongue Soft palate Hard palate	2, 9, 10, 12,13, 14,20, 23, 22, 28, 29, 30, 31, 33, 35, 39, 40, 37
Geographic tongue	SARS-CoV-2	Tongue	12

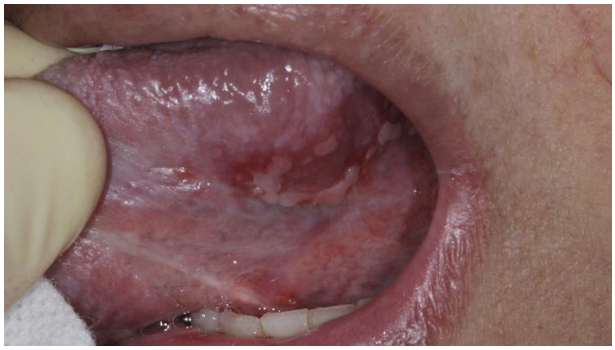


Fig 3: Lingual ulceration in a Covid-19 positive patient [16]

Periodontal lesions

Periodontal diseases are represented by gingivitis, ulcerative gingivitis and ulcerative periodontitis (Table IV).

Table IV: Periodontal diseases

Types of lesions	Types of viruses	Most frequent locations	References
Gingivitis	HSV-2 EBV Paramyxoviridae HIV SARS-CoV-2 Hepatic viruses	Gum	2, 9, 10, 12, 13, 14, 16, 19, 20, 24, 25, 26, 28, 29, 31, 33, 35, 36, 37, 38, 40, 67
Ulcero-necrotic gingivitis	HIV SARS-CoV-2 Hepatitis viruses	Gum Interdental papilla	2, 9, 12, 13, 14, 16, 19, 20, 24, 25, 28, 29, 31, 33, 35, 37, 40
Ulcero-necrotic periodontitis	HIV SARS-CoV-2 Hepatic viruse	Gum Interdental papilla Alveolar bone	2,9, 10, 12,13, 14, 16, 19, 20, 24, 25, 29, 31, 33, 35, 28, 37,40, 68

Erythematous lesions

Erythematous lesions are represented by hematomas, erythema, enanthemata and petechiae (Table V).

Table V: Erythematous lesions

Types of lesions	Types of viruses	Most frequent locations	References
Hematoma	Hepatic viruses	Cheeks Veil of the palate Lips Tongue Oral floor	**12**
Erythema	HSV-2 VZV Paramyxoviridae HIV SARS-CoV-2	Gum Lips Tongue Cheeks Palatal Vault Palate Veneer	**2,10, 12, 13,14, 16, 18, 20, 22,23, 29, 30, 34, 39**
Enema	Paramyxoviridae Parvovidae SARS-CoV-2	Palatal Vault Palate Veneer	**20, 34**
Petechiae	EBV Hepatic viruses HIV SARS-CoV-2	Posterior location of the oral cavity	**2,13, 20, 22,23,29, 30, 33, 35, 39**

DISCUSSION

Several types of non-tumor lesions of the oral mucosa related to viral infections have been reported in the literature [41-44]. These non-tumor lesions are diverse and varied, depending on the type of virus involved, ranging from surface color variation to substance loss. In viral infections, damage to the oral mucosa may begin with elementary lesions of the macular and/or papular type, sometimes developing on an erythematous base, which will rapidly transform into vesicles due to the cellular necrosis caused by the viral invasion [45, 46]. These vesicles will then transform into bullae which will then rupture leaving in place losses of substances which may be superficial (erosions) and/or deep (ulcerations) [45-47].

Several viruses have been implicated in the occurrence of these lesions, the most commonly reported being CMV, herpes viruses, EBV, enteroviruses, coxsackievirus, HIV and SARS-CoV2 [45, 46, 48].

The jaundice noted in the oral mucosa is thought to be due to excess bilirubin in the plasma and tissues. Indeed, the intensity of the staining is a function of the serum bilirubin level [12]. The viruses involved in the occurrence of jaundice of the oral mucosa are the Hepatitis viruses [12].

In viral infections, the most commonly reported erythematous lesions are hematomas, erythema, enanthemata and petechiae [33]. All these lesions are related to disorders of hemostasis due to

viral infections [49]. Indeed, hematomas and petechiae are often encountered in viral infections affecting the liver, leading to hepatitis dysfunction and a deficit in the production of vitamin K-dependent coagulation factors [12, 13]. These oral manifestations of haemorrhagic syndromes, encountered in viral infections, would be linked either to vascular damage (vasculitis), or to destruction of blood platelets and/or coagulation factors, or to activation of fibrinolysis factors [49].

Furthermore, vascular damage may be deep (hematomas, erythema) or superficial (petechiae, enanthemata) [49]. These lesions can be found anywhere on the oral mucosa [50]. In addition to erythematous lesions, viral infections may also cause leukoplakia. The most reported leukoplakic lesions are hairy leukoplakia, cheilitis and candidiasis [51, 52, 53]. Indeed, co-infection of EBV, HPV and Candida albicans has been reported in the occurrence of leukoplakia lesions [54]. The severity of the lesions depends on the local immune response, the EBV gene expression profile and environmental factors [55, 56]. EBV is mainly responsible for the occurrence of leukoplakic lesions of the oral mucosa due to its high replication rate [54, 56, 57, 59, 60]. This replication is more marked in immunocompromised subjects, leading to the occurrence of hairy leukoplakia [54, 59, 61]. As for candidiasis, it is an opportunistic infection, linked to the proliferation of Candida albicans due to the failure of local immune defense mechanisms by the qualitative and quantitative alterations of saliva. Infection with Candida albicans will favor the development of candidiasis, the severity of which will depend on the level of failure of the immune defense mechanisms and the agent responsible for the viral infection [44]. Often observed in patients infected with HIV or SARS-COV2, they can be pseudomembranous and/or erythematous [40,44]. Leukoplakic lesions are mostly found on the tongue and can be observed on the entire oral mucosa [55, 59, 60, 62].

Apart from variations in surface appearance, viral infections can lead to vesicular and/or bullous lesions in the oral mucosa. Several viruses including HSV-1, Coxsackie A16 and VZV have been implicated [33]. These vesicular and bullous lesions during viral infections are often due to necrosis of the basal and suprabasal epithelial cells leading to the subsequent formation of intra- and subepithelial bullae [63, 64]. Indeed, during the incubation period, the viruses will proliferate inside the macrophages provoking a specific humoral and cell-mediated immune response leading to the necrosis of the infected cells. Subsequently, the vesicles and/or bullae will rapidly rupture, leaving in place a loss of substances that may be deep and/or superficial [63, 64]. This is particularly true of erosions and ulcerations, of which the aphta is a part, related to viral infections [43, 65]. Depending on the type of lesion, the viruses involved are different. In erosions, which are superficial losses of substance involving only the epithelium, the most commonly reported viruses are Coxsackie A and B, HSV-1, VZV and HIV [65, 66]. Ulcerations, which are discharges reaching the chorion, are often due to HSV-1, HSV-2, VZV, CMV [42, 43, 48], coxsackie virus [43], SARS-CoV-2 [44], EBV [48, 66, 67] and HIV [66].

These discharges are often preceded by vesicles, which may be single or multiple, and which subsequently rupture, leaving ulcerations with polycyclic edges [42, 43, 65, 66]. This could be explained by the fact that the viruses use the genetic material of the cells in order to multiply, thus destroying the cells [41, 43, 66]. These lesions are often due to immune mediated mechanisms [43]. In some viral infections, such as those related to SAR-Cov2, these ulcerations and/or erosions are often associated with areas of tissue necrosis [44]. These losses of substance can be found anywhere in the oral mucosa [65, 66].

In addition, periodontal lesions have been reported in viral infections ranging from simple to very aggressive [7, 68, 69]. In addition to the qualitative and quantitative alterations of saliva and gingival fluid by viruses, the bacteria involved in the occurrence of periodontal diseases will cause a reactivation by epigenetic regulation of certain viruses such as those of herpes (HSV), EBV, CMV, and hepatitis viruses [7, 68, 69]. This explains the existence of synergy reported by Khinda between viruses and bacteria in the initiation and progression of periodontitis [69]. Viruses such as EBV, CMV are incriminated in severe periodontitis including gingivitis and ulcerative periodontitis [83, 70, 69, 51, 50].

On the other hand, for herpes viruses, the intensity of infection is correlated to the loss of attachment and the depth of pockets on probing [69]. Indeed, the replication of the virus associated or not with the alteration induced by the virus on the host immune defenses will favor an increased aggressiveness of the resident bacterial pathogens [70].

CONCLUSION

Viral infections are diverse and varied. Some of them can cause lesions of the oral mucosa ranging from surface lesions to malignant tumors. Indeed, lesions of the oral mucosa can be the first symptoms or accompany the other clinical manifestations.

These lesions of the oral mucosa are similar to lesions encountered in certain pathologies. This can pose diagnostic but also therapeutic difficulties. For most of these lesions, a rigorous clinical examination allows a good diagnostic orientation which must always be confirmed by biological examinations. Indeed, the diversity of these lesions would be linked to the

diversity of the pathogens whose powers of invasion are different.

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