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Recurrent intraoral HSV-1 infection: A retrospective study of 58 immunocompetent patients from Eastern Europe

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Abstract

Objectives. To revise the clinical features of the recurrent intraoral herpetic infection (RIOH) with respect to precipitating factors, demographic, clinical features and outcome.

Study design. Fifty-eight, unrelated Caucasian, immunocompetent patients with positive laboratory test for intraoral Herpes simplex virus infection were studied.

Results. The mean age in the women's group (n=42) was 41.23 years (± 21.73) and in the men's group was 32.25 years (± 15.68). Possible trigger factors were identified in 9 cases (15.5%). General symptoms were noted in 20 cases (34.48%). Most of patients in this study presented multiple lesions. 14 patients had vermillion lesions associated with intraoral lesions. In most of the cases both fixed and mobile mucosa was concomitantly involved. Treatment was prescribed in order to control the symptoms and to shorten the evolution with minimal side effects.

Conclusions. Intraoral secondary herpetic infection could be polymorphous and sometimes associated with general symptoms. The recognition of its atypical features may prevent unnecessary and costly investigations and treatments for unrelated though clinically similar-appearing disorders.

Key words: *Intraoral, recurrent, HSV-1, diagnosis, treatment.*

Introduction

Infection caused by the Herpes simplex virus (HSV) represents one of the more common infections of the oro-facial area (1). Herpes simplex virus type-1 (HSV-1) is probably the more widespread strain of the Herpes virus family, being considered to give rise to infection "above the waist". Following infection and local replication at mucosal surfaces, HSV-1 enters sensory nerve endings and is then transported by retrograde axonal transport to the neuronal cell bodies. Here, a more restricted replication cycle occurs, most often culminating in a latent infection of these neurons. Latency allows the maintenance of the viral genome in a non-pathogenic and non-replicate form and serves as a reservoir for later viral attack of the host (2,3). Reactivation of the virus in the sensory ganglia causes cutaneous and mucocutaneous manifestation of recurrent herpes. The lesions typically occur on the mucocutaneous junction of the face, usually on the lips. Recurrent intraoral HSV-1 infection (RIOH) is much less common and thought to be rare in otherwise healthy patients (4,5). Seldom have cases of RIOH been fully described (6), possibly because they are frequently undiagnosed.

In this retrospective report we reviewed different features of 58 Romanian patients with RIOH managed in an oral medicine unit.

Patients and Methods

The case records of all patients who had been initially referred to the Oral Medicine Unit of the Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, for the diagnosis and management of RIOH, from 1997 to 2007, were reviewed.

The charts were searched for all the data concerning age and gender, smoking habits, alcohol consumption, presence of systemic disease and use of any drugs. Patients with a recognized history of immunodeficiency or other systemic condition related to it (malignancies, history of transplants, HIV infection, chronic infections, systemic immunosuppressive treatment or corticosteroid therapy) were excluded. Cases with intraoral ulcerations or intraoral and vermillon border lesions that were cultured positive for HVS or positive Tzanck cytology were enrolled. Two independent Oral Medicine specialists (S.T., and P.A.) and a Dermatologist (M.T.) examined the charts. Patients were referred both by dentists and physicians. The following information was retrieved: main complaints, general symptoms, lymphadenopathy, duration, triggering factors for reactivation of HVS, concomitant presence of herpes simplex labialis, sites of oral involvement, size, number of the lesions and presence of the vesicles at the first visit.

Two main complaints were observed: pain and burning. Pain was divided on a scale from 0-absent, 1-moderate, 2-severe. As burning was difficult to evaluate, we restrained the term to a single degree.

As in most of the cases the lesions were multicentric, presenting multiple locations, we used two methods for a clinical evaluation: a) topographical localisation (sites involved); b) extent of the eruption: the extent of the lesions was classified as: "small" if 1-2 different oral zones were involved, "medium" when 3 different zones were involved, and "wide" when more than 3 different zones were involved.

The location of the lesions was based on clinical criteria recommendations of the World Health Organization (7).

Laboratory confirmation was performed by either PCR (30 cases), or immunoflourescence (10 cases) (8-10). As viral detection is not covered by the social security system, not all the patients could afford its cost. In 18 cases, Tzanck cytology was used as reliable laboratory method (11,12). Samples were examined by the same pathologist (L.C.).

-*Data analysis*

All different data collected from each patient were analyzed using descriptive statistics. Continuous variables are expressed as mean ± SD. For the ordinal variables we used nonparametric tests (Mann-Whitney, for comparison and Spearman correlation, for correlation). Statistical analysis was performed by SPSS® software (SPSS for Windows, version 16, SPSS inc, Chicago, IL, USA). Significant levels were calculated for $p<0.05$.

Results

-*Demographic features*

Eighty-one charts were selected. A number of cases were excluded from the study: 18 cases with incomplete data, and 5 cases with only labial or perioral lesions. Finally, the study group comprised 58 unrelated Caucasian patients (42 female and 16 male). The mean age in the women's group was 41.23 years (±21.73) and in the men's group was 32.25 years (± 15.68). The majority, i.e. 18 (31.03%) of these, was in the 3rd decade of life (Fig. 1).

-*Clinical oral profile*

Most of the patients presented themselves in the first 4 days (n=22), or after 7 days of the onset (n=18). Possible trigger factors were identified in 9 cases (15.5%). Of these, 3 patients reported a history of undergoing dental procedures and/or excessive tooth brushing in the preceding day of the eruption. Four patients reported the onset after spicy or conservated food. In 2 other cases, the eruption occurred after a febrile infection (influenza, acute tonsilitis). Other precipitating factors, typically associated with the reactivation of herpes labialis, including sunlight, menses and stress, were not observed in our series. In any patient from this series, the intraoral infection was not preceded by other local symptoms (tingling or burning).

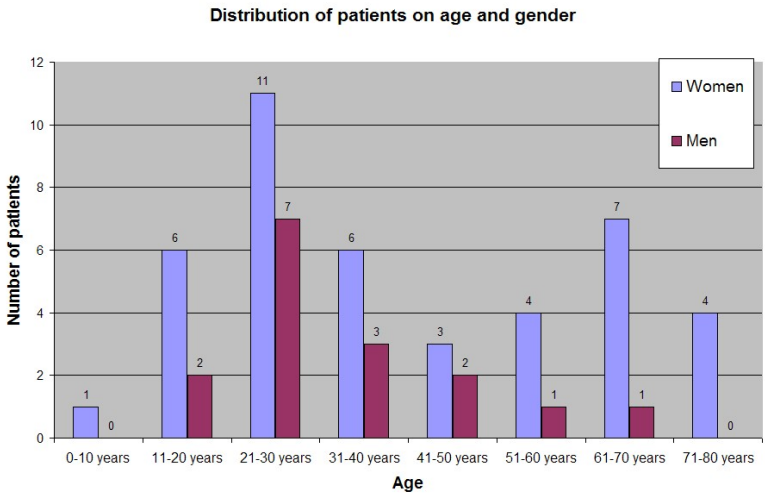

Fig. 1. The distribution of cases on gender and age.

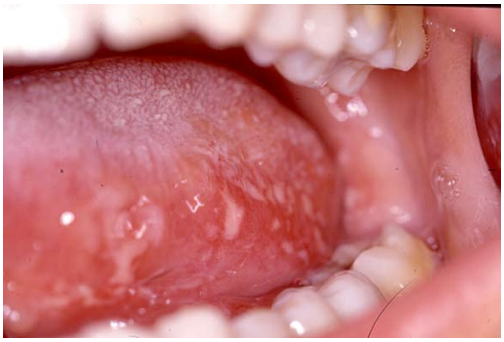

Fig. 2. A) Widespread RIOH eruption on both keratinized and non keratinized oral mucosa in 43-year-old male patient.

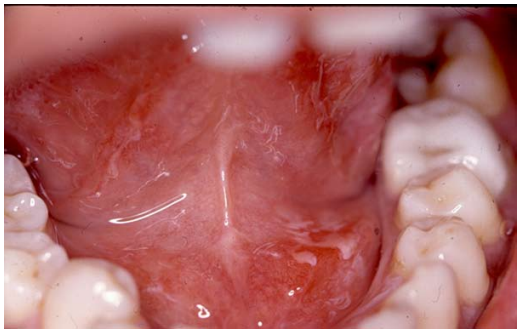

Fig. 2. B) Widespread RIOH eruption on both keratinized and non keratinized oral mucosa in 43-year-old male patient.

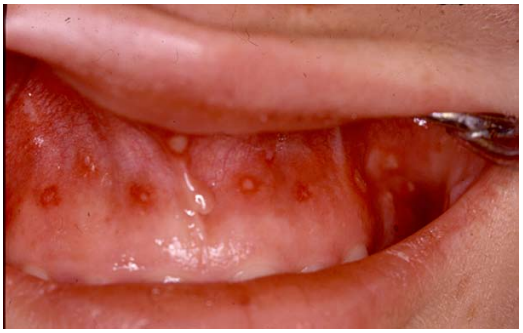

Fig. 3. A) Widespread RIOH eruption on both keratinized and non keratinized oral mucosa in 25-year-old female patient.

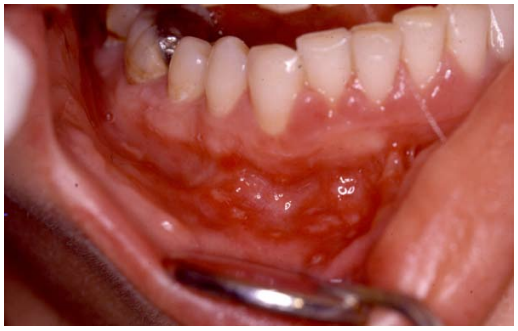

Fig. 3. B) Widespread RIOH eruption on both keratinized and non keratinized oral mucosa in 25-year-old female patient.

Table 1. Clinical characteristics and symptoms of RIOH lesions at initial visit.

Scale of pain and burning reported	**No. of cases**	**Percentage (%)**
0-absent	0	0
1-moderate	36	62.1
2-severe	3	5.2
3-burning	19	32.7
No. of ulcerations	**No. of cases**	**Percentage (%)**
1 ulcers	4	6.9
2-4 ulcers	17	29.3
More than 4 ulcers	37	63.8
Size of ulcerations	**No. of cases**	**Percentage (%)**
1-5mm	35	60.3
5-10mm	16	27.7
1-2cm	6	10.3
>2cm	1	1.7
Extent of the eruption	**No. of cases**	**Percentage (%)**
Small 1-2 areas	36	62.06
Medium 3 areas	10	17.24
Wide more than 3 areas	12	20.60

General symptoms, before or in association with intraoral eruption, were noted in 20 cases (34.48%). Of these, 7 cases had moderate fever (e.g. 37-39ºC) and 12 patients noted cervical lymphadenopathy about 24 hours before the recurrences.

The clinical appearance and main complaints are presented in table I.

In all the patients, ulcers were present. The lesions were shallow erosions with irregular borders covered by yellowish-white deposits surrounded by an erythematous halo. In some cases the ulcerations coalesced in large irregular ulcers of more than 1 cm. In other cases, especially when present on non-keratinized mucosa, the ulcers present a regular, round or ovoid shape very similar to RAS (Fig. 2). In 18 cases (31.03%) concomitant ulcers and vesicles were observed. All the patients in this group were within the first 7 days from the onset. Some patients have noticed the presence of these vesicles at the moment of the onset, before the first visit.

In most of the cases the lesions were smaller than 5 mm. However, large ulcers resulting from the coalescence of smaller ones have been observed. No correlation has been found between the ulcer's size and the duration of the disease ($r = 0.167$, $p=0.209$).

Most of patients in this study presented multiple lesions (Fig. 3). The extent of the lesions as a mean to evaluate the intensity of the lesion is presented in table 1. An important number of cases presented a wide intraoral eruption. No correlation was observed between the extent of the lesions and the associated pain or burning sensation ($r = 0.077$, $p=0.564$). Conversely, in the three cases of patients proclaiming severe pain, a widespread oral eruption was observed. A correlation has been found between the extent of the lesions and the general signs in the 12 patients with widespread intraoral eruptions (more than three areas involved) ($p=0.03$).

The labial mucosa was the most commonly affected (51.7%) (Table 2). In 14 patients vermillion border involvement associated with intraoral lesions was observed. In most of the cases, both fixed and mobile mucosa was concomitantly involved. Mobile mucosa alone was involved in 17 cases, and finally, the keratinised mucosa in 14 cases. The attached maxillary mucosa was much more affected than the mandibular one (21 vs 11).

-*Treatment*

Treatment was prescribed in order to control the symptoms and to shorten the evolution with minimal side ef-

Table 2. The topographical distribution of lesions and typed of mucosa involved.

Regions involved	**No. of lesions**	
Labial mucosa	30	
Hard palate	24	
Attached gingiva, maxillary	21	
Tongue	20	
Buccal mucosa	15	
Vermillion in association with other intraoral lesions	14	
Attached gingiva, mandibular	11	
Soft palate	7	
Floor of mouth	4	
Distribution according the type of mucosa	**No. of cases**	**Percentage (%)**
Fixed and mobile mucosa	27	46.6
Mobile mucosa	17	29.3
Fixed mucosa	14	24.1

fects. For topical treatment, we used aciclovir 5% cream, to be applied every 4 hours for 5 days in all cases with vermillion border lesions. Systemic aciclovir (200 mg po 5 times daily for 5-7 days) was administered in all 12 cases of widespread infections with a follow up period of two weeks. Topical treatment alone with viscous lidocaine (2%) was applied as a palliative agent in all cases with important oral complaints (26 cases) and as adjuvant for the systemic treatment.

Discussion

Clinically detectable secondary infection arises in 20 to 40% of HSV-1 seropositive individuals (13,14). Approximately 25% of facial herpes recurrences do not progress beyond the prodromal or papular stage (15). The lesions of secondary infection are usually red macules that rapidly become vesicular, being very infectious at this stage, later forming pustular-scabs and ulcers. Healing occurs within 1 to 10 days from initial symptoms (4,8,15).

It has been proposed that RIOH are definitively less common than herpes labialis, usually arising on keratinized surfaces, such as the hard palate and attached gingiva. They are few in number, small, mildly painful, and last less than 10 days (6,12,16). The results of this study support the idea that RIOH is not so rare in otherwise healthy subjects as previously mentioned (16,17).

The clinical features of patients in our survey share many similarities with those reported previously, but we also observed some essential differences.

Most of the patients presented themselves in the first days or after 1 week of the onset. An explanation of this observation could be that some patients come earlier due to the local discomfort, and others when they notice that the lesions do not disappear in short time. Most of the patients in this group proclaimed moderate pain and/or burning sensation. Consequently, it is to be supposed that some patients with RIOH could be asymptomatic and unaware of their disease, being thus a source of contamination. The patients should be advised of their condition in order to prevent spread of the virus to eyes or genitals, or spread of the virus to others (6,8). Some patients reported dental procedures before the onset. The small crops of ulcers can follow a palatal local anaesthetic injection (18,19).

The presence of the vesicles was not as rare as previously reported (6). We noticed them in about one third of the cases. This clinical sign can be a suggestive hint when doing a differential clinical diagnosis with recurrent aphthous stomatitis (RAS). The involvement of the labial mucosa was found as the most commonly reported. Intraorally, we found no rule of distribution of the lesions in RIOH, even if we have noticed a predilection for hard palate and alveolar ridge. Unlike other studies, most of the patients in this group presented multiple lesional locations. The presence of concomitant herpes simplex labialis, observed in about one quarter of cases could be a reliable indicator. As previously reported (6,16), the ulcers of RAS occur almost exclusively on nonkeratinized mucosa. However, the clinical features of RIOH are in some instances clinically very close to RAS especially when present only on mobile mucosa. Besides, patients afflicted with RAS commonly, but inaccurately, perceive the cause of their ulcers as HSV infection; of identical impact, patients with RIOH often are not accurately identified (6).

The involvement of fixed mucosa (alone or in association with nonkeratinized mucosa) in about 70% of cases in this series is in accord with previous studies and it is a definitive sign of the disease.

Conversely, the presence of the ulcerations of the mobile mucosa alone could be very close to RAS. At the same time, these lesions could raise the problem of an atypical herpetic eruption found in immunosupressed patients (6,8). Rarely, in some cases RIOH could have a long evolution even in immunocompetent patients (3 cases in our series). Thus RIOH should be considered a source of intraoral chronic ulcerations on the mobile mucosa in immunocompetent patients. Detailed history and laboratory work-up is mandatory in all those cases (12,17). Moreover, RIOH must be differentiated from other ulcerative diseases (20) such as Coxsackie virus infection, infectious mononucleosis, erythema multiforme minor, acute necrotising ulcerative gingivitis (ANUG), ulcers in periodic syndromes (21), Varicella Zoster Virus infection and some unusual cases of desquamative gingivitis. Despite previous opinions (12), in some instances, secondary herpetic eruptions may be widespread and associated with general symptoms, and also mimicking thus a primary herpetic gingivostomatitis. Such cases have been previously reported (22). The occurrence of general symptoms in RIOH has rarely been reported before. This probably could be explained because of the possible greater viremia, which develops in these patients, perhaps greater than in those with only labial manifestation.

Retrospective observational studies may have different limitations; however, we added new information regarding the intraoral features of HSV-1 recurrent infection in immunocompetent patients, which has rarely been published. Because it has been reported that HSV-1 affects up to 75% of the general population (14), it is expected that a noteworthy number of people, far greater than that detailed in literature, develop RIOH and not only labial lesions.

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