Research Article

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Recurrent Aphthous Ulcers: Experience from a Tertiary Care Center

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Abstract

Background: The frequency of recurrent aphthous ulcers (RAU) and their relationship with comorbidities has been scarcely described.

Methods: We conducted a retrospective analytical study of patients with a presumptive diagnosis of RAU, in order to know the frequency of misdiagnosis of RAU, to delineate the clinical and biochemical characteristics of RAU, and to analyze their correlation with systemic diseases. Three groups of recurrent ulcers were analyzed: a) RAU, b) RAU associated to Behçet’s disease, and c) other recurrent ulcers misdiagnosed as RAU (OU). We recorded clinical and laboratory data. Statistics included Mantel-Haenszel chi square test, Kruskal-Wallis test, and Student’s *t* test.

Results: A total of 141 patients (106 women) were referred with a presumptive diagnosis of RAU: 56 cases (39.7%) with RAU; 10 (7.1%) with RAU in Behçet’s disease, and 75 (53.2%) with OU. RAU subjects presented a lower frequency of rheumatologic diseases than patients with Behçet’s disease ulcers [30.4% vs 70.0%; (*p*=0.03)] and patients with OU [30.4% vs 54.7%; (*p*=0.007)]. Additionally, immune deficiency was less common among patients with RAU in comparison to Behçet’s disease [3.6% vs 40.0%; (*p*=0.003)] and OU [3.6% vs 28.0%; (*p*<0.001)].

Higher levels of serum leukocytes were seen in Behçet’s disease [median=8.9 (range 5.3-9.7) × 10³ cells/mm³] when compared to RAU [median=6.0 (range 3.2-21.2) × 10³ cells/mm³] and OU [median=6.0 (range 2.3-14.8) × 10³ cells/mm³] (*p*<0.04).

Conclusions: Misdiagnosis of RAU was frequent; an individual pattern of association to specific groups of systemic diseases was observed in each studied group of recurrent ulcers. RAU and Behçet’s disease ulcers showed clinical and laboratory differences.

Keywords: Recurrent aphthous ulcers; aphthous-like ulcers; recurrent aphthous stomatitis; systemic diseases; mouth diseases

Introduction

Oral aphthae are ulcerative, inflammatory lesions of the mucosa with specific clinical features and different etiologies. Oral aphthae may be isolated or present as part of systemic or specific diseases of the oral cavity [1,2]. They are painful, thus hindering food ingestion, which in turn may cause great morbidity [3,4]. When these are recurrent, they are known as recurrent aphthae, recurrent ulcers, canker sores, recurrent aphthous stomatitis, or recurrent aphthous ulcers (RAU) [5].

The prevalence of RAU may vary widely (1-66%) among adults [6]. RAU are considered as one of the most common oral mucosa disorders; nevertheless, they are poorly understood and have not been clearly described. Currently, no satisfactory definition of this entity has yet been published [7-10]. RAU diagnosis is essentially made on a clinical basis, since no specific histopathologic or laboratory tests are available for this purpose [11]. Clinically, RAU are defined as self-limited recurrent oral mucosal ulcers located to the non-masticatory mucosa; they may be round or oval-shaped, featuring a white-yellowish, white-greyish, or yellow-greyish surface; and are surrounded by an erythematous halo [8]. However, the differences between oral aphthous ulcers and other types of oral ulceration are still unclear; thus, it is difficult to recognize RAU with the use of a non-discriminatory criteria [12].

Local and systemic factors such as stress, hormones, trauma, microorganisms, food, food allergy [13], drugs, immunological diathesis, genetic predisposition [9], and nutritional deficiencies [14,15] seem to play an important role on the development of RAU [2,16]; additionally, the etiology of RAU has been considered multifactorial [17].

Nonetheless, the main cause of RAU has not been explained yet; therefore, no curative or preventive therapy for the recurrence of these ulcers has been proposed [18]. Currently, the available treatments only reduce the frequency or severity of the lesions [18,19], being symptomatic at best [20].

RAU is a diagnosis of exclusion, therefore a thorough workup to narrow the differential is needed [21]; consequently, misdiagnosis of RAU is frequent [22]. Although RAU is a common finding that may accompany a number of systemic diseases, such as Behçet's disease (BD) [1], the frequency of RAU and their relationship with comorbidities has been scarcely described. Thus, the objectives of this study were: 1) to establish the prevalence

of RAU in adult subjects with presumptive diagnosis of RAU who attended our specialized outpatient Oral Pathology Clinic; and 2) to determine the clinical and laboratory profile of RAU and their relationship to systemic disease.

Materials and Methods

We performed a retrospective, cross-sectional, analytical study at the outpatient Oral Pathology Clinic. The study was approved by the institutional review board (C.E.I. DER-2156-17/17-1) of the National Institute of Medical Science and Nutrition "Salvador Zubirán", in Mexico City.

We included patients >18 years referred with a presumptive diagnosis of RAU who attended the Outpatient Oral Pathology Clinic from July, 2001 to January, 2014.

An oral pathologist (LEP) classified the study subjects in the following groups: a) confirmed diagnosis of RAU, and b) other types (OU) of recurrent ulcers (ulcerations referred as RAU or aphthous-like lesions, that did not fulfill the clinical and/or histological criteria for RAU). We considered the international definitions of RAU to establish the clinical and microscopic diagnosis of RAU [8]. The diagnosis of cases categorized as OU were confirmed by histological and/or biochemical analysis, with the exception of ulcers secondary to trauma.

Epidemiologic, anthropometric, clinical, and laboratory variables were considered, such as age, sex, main systemic disease, previous management of RAU, type of RAU, site of lesions, symptoms, tobacco use, alcohol consumption, blood levels of iron, vitamin B₁₂, folic acid, leukocytes, lymphocytes, platelets, hemoglobin, glycosylated hemoglobin, and glucose. Laboratory data matching ($\pm$ 3 months) the initial consultation were drawn from the medical charts.

In order to assess symptoms induced by the ulcers, the following scale was used: no pain; slight, if pain was minimal or burning; moderate, if pain was significant but not enough to limit food ingestion; and severe, if pain was enough to limit food ingestion. Tobacco use was assessed according to its presence and intensity as occasional (<5 cigarettes/week), mild (1-4 cigarettes/day), moderate (5-19 cigarettes/day), and heavy ($\geq$ 20 cigarettes/day); and whether the patient was a former smoker (quitting smoking $\geq$ 3 months). In order to facilitate the statistical analysis, the severity of smoking habit was dichotomized as occasional/mild, and moderate/intense. Alcohol consumption was considered as intense (intoxication $\geq$ 1 time/week), occasional (intoxication <1 time/week) or negative. We

considered a history of oral ulcer management whenever the patient had received treatment (≤ 30 days) before the first assessment at the outpatient Oral Pathology Clinic.

For analytical purposes, RAU were subdivided into two groups: subjects with RAU, and patients with RAU in Behçet's disease [23,24], considering their immunological and clinical differences [25,26].

We excluded cases whose medical charts had no follow-up notes, were discharged from the outpatient service, or were lost to follow-up from the outpatient Oral Pathology clinic.

Results were analyzed using SPSS v.20 and Epi Info™ statistical packages. Oral ulcers were analyzed by gender, tobacco use, alcohol consumption, and comorbidities, using the extended Mantel-Haenszel chi square test; by age using the Kruskal-Wallis test; and by laboratory values using Student's *t* test. We excluded variables from statistical analysis when missing information of cases was $\geq 80\%$ in laboratory tests or $\geq 50\%$ in clinical variables. Medians (md) were used to describe age and laboratory values. A *p* value ≤ 0.05 was considered as statistically significant.

Results

During the study period, there were a total of 5,845 follow-up visits to the Oral Pathology Clinic, corresponding to a total of 1,975 patients. We detected oral mucosal ulcerations in 250 patients (12.7%), and 141 (7.1%) of these cases were referred as potential RAU.

Of the total of patients referred as presumptive RAU ($n=141$), 66 (46.8%) met the criteria for the diagnosis of RAU: 56 cases (39.7%) with RAU, and 10 (7.1%) in BD. A total of 75 (53.2%) cases corresponded to OU. The epidemiologic, clinical, and laboratory characteristics of the patients are detailed in tables 1 and 2. The diagnosis of OU are described in table 3. The observed findings for each type of ulceration are described in table 4.

Ulcerative lesions were more frequent in women than in men [106 (75.2% vs 35 (24.8%) $p<0.001$] in all the studied groups (Table 1). A significant difference could be observed on the age of presentation in all ulcerative lesions in men [md=35 (range 19-74) years old] when compared to women [md=45 (range 18-82) years old; $p=0.009$]; likewise, the median age was significantly greater in the group of patients with OU (Table 1) when compared to RAU (49 vs 36 years old; $p<0.001$), or with BD (49 vs 36 years old; $p=0.01$).

As observed in table 1, patients with RAU were less

frequently affected by synchronic rheumatologic diseases when compared to patients with BD [30.4% vs 70.0%; ($p=0.03$)] or OU [30.4% vs 54.7%; ($p=0.007$)]; also, the rate of immunodeficiencies was less frequent among patients with RAU when compared to patients affected by BD [3.6% vs 40.0%; ($p=0.003$)] or OU [3.6% vs 28.0%; ($p<0.001$)]. Patients presenting RAU were less likely to be affected by nephropathies 1.8% vs 13.3%; ($p=0.02$)] and thyroid derangements [0% vs 14.7%; ($p=0.002$)] than those having OU.

The median concentration of blood leukocytes (Table 2) was greater in patients with BD [8.9 (range $5.3-9.7$) $\times 10^3$ cells/mm³ ($p=0.04$)] in comparison to patients presenting with RAU [6.0 (range $3.2-21.2$) $\times 10^3$ cells/mm³] or OU [6.0 (range $2.3-14.8$) $\times 10^3$ cells/mm³]. No other relevant associations were found.

Discussion

The prevalence of RAU may be highly variable, but at least 20% of the general population may be affected at some point of life [8]. In our results, RAU comprised three percent of all Oral Pathology outpatient consults. Only 46.8% of the cases referred to the clinic as recurrent ulcers were classified as RAU; RAU mainly affected women and young adults, as thoroughly described elsewhere [27,28].

Our results show a high rate of recurrent ulcers that do not correspond to an aphthous morphology, although patients were referred with this diagnosis; this may imply that a high percentage of recurrent ulcerative conditions may partially mimic RAU [22,29], or clinicians are not acquainted with RAU and their differential diagnosis, hence the frequent misdiagnosis and mistreatment of these lesions.

The RAU in BD are part of this systemic disease, clinically diagnosed by the presence of major criteria such as RAU, genital ulcerations, ocular inflammation (conjunctivitis, uveitis or iritis), cutaneous lesions (pseudofolliculitis, folliculitis, erythema nodosum), and positive pathergy test (skin hyper reactivity). Minor criteria include the presence of articular lesions, central nervous system derangements and/or vascular/cardiovascular lesions. The disease is diagnosed by the presence of RAU and two major criteria or two major and two minor criteria [24]. Previous authors, assert that the late onset of mouth lesions that resemble RAU may suggest the possibility of developing a more complex derangement such as BD [11]; and that oral aphthae in patients with BD are usually minor RAU. However, our findings demonstrated that both RAU and

Table 1: Epidemiologic and clinical characteristics of the studied patients (n=141)

Characteristics	Aphthae		Other ulcers ^a		Behçet's disease	
	(n=56)		(n=75)		(n=10)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	38	(67.9)	61	(81.3)	7	(70)
Male	18	(32.1)	14	(18.7)	3	(30)
AGE/years (Md/Range)	36	(19-76)	49	(18-82)	36	(18-55)
Tobacco Use						
Never	25	(44.6)	43	(57.3)	5	(50)
Occasional	8	(14.3)	1	(1.3)	1	(10)
Mild	2	(3.6)	7	(9.3)	1	(10)
Moderate	3	(5.4)	2	(2.7)	-	-
Heavy	2	(3.6)	2	(2.7)	-	-
Past smoker	-	-	11	(14.7)	3	(30)
Missing data	16	(28.6)	9	(12)	-	-
Alcoholism						
No	41	(73.2)	56	(74.7)	7	(70)
Occasional	15	(26.8)	19	(25.3)	3	(30)
Comorbidities						
Rheumatologic disease ^b	17	(30.4)	41	(54.7)	7	(70)
Immunodeficiency ^c	2	(3.6)	21	(28)	4	(40)
Gastrointestinal disease ^d	7	(12.5)	14	(18.7)	1	(10)
Malignant neoplasiae	4	(7.1)	11	(14.7)	-	-
Hematologic	4	(7.1)	10	(13.3)	-	-
Respiratory	5	(8.9)	8	(10.7)	-	-
Dyslipidemia	5	(8.9)	7	(9.3)	-	-
Nephropathy	1	(1.8)	10	(13.3)	1	(10)
Thyroid disease	-	-	11	(14.7)	1	(10)
Arterial hypertension	3	(5.4)	7	(9.3)	-	-
Dermatologic	1	(1.8)	8	(10.7)	1	(10)
Diabetes mellitus	1	(1.8)	4	(5.3)	-	-
Neurologic	1	(1.8)	4	(5.3)	-	-
Hepatic	-	-	4	(5.3)	-	-
Obesity	-	-	3	(4.0)	-	-
Urologic	-	-	2	(2.7)	-	-
Nutritional	-	-	1	(1.3)	-	-

Md = Median

a: Include traumatic ulcers, pemphigus vulgaris, nutritional deficiencies, drug side-effects, herpes simplex virus infection, lupus erythematosus, lichenoid reactions, vasculopathy, syphilis, leukoplakia and bacterial infection. b: Rheumatologic diseases include Mikulicz's disease, lupus erythematosus, rheumatoid arthritis, Behçet's disease, Sjögren's syndrome antiphospholipid syndrome, and osteoarthritis.

c: Immunodeficiency includes HIV-infection, primary immunodeficiencies, and transplant patients.

d: Gastrointestinal diseases include inflammatory bowel disease, primary biliary cirrhosis, reflux, and gastritis.

e: Malignant neoplasia includes non-Hodgkin's lymphoma, multiple myeloma, squamous cell carcinoma, thyroid carcinoma, malignant meningioma, plasmacytoma, and myelodysplastic syndromes.

Table 2: Serological data of the studied patients

	Aphthae		Other ulcers		Behçet's disease		
Laboratory analysis	(n=56)		(n=75)		(n=10)		
	(Md)	(Range)	(Md)	(Range)	(Md)	(Range)	p value^a
Leukocytes K/ μ L (n=106)	6	(3.2-21.2)	6	(2.3-14.8)	8.9	(5.3-9.7)	0.04
Lymphocytes K/ μ L (n=95)	29.7	(6.1-50.0)	27.4	(3.3-50)	24.3	(12.4-39.6)	NS
Hemoglobin g/dL (n=97)	14.1	(5.2-17.7)	13.7	(4.9-16.9)	13.1	(11.7-15.6)	NS
Platelets K/uL(n=100)	255	(86-519)	265	(101-429)	272	(207-406)	NS
Glucose mg/dL(n=77)	90	(63-137)	88	(21-123)	94	(86-101)	NS
Hemoglobin A1c % ^b (n=16)	5.4	(4.9-6.6)	5.6	(5.3-7.3)	5.5	(-5.5)	-
Iron μ g/dL ^b (n=26)	75	(17.5-154.0)	79.5	(23-115)	104	(-104)	-
Vitamin B12 pg/mL(n=39)	501	(228-14673)	468	(212-3974)	545	(146-906)	NS
Folic acid ng/mL ^b (n=30)	8.7	(4.1-45.9)	10.4	(6.9-19.6)	7.2	(6.3-8.1)	-

Md=median

a: Student's t test

b: Excluded from the statistical analysis

BD ulcerations may be more frequently observed in young adults than in OU patients [9]; and most of our cases with BD showed major lesions, as stated by others [5]. On the other side, despite the morphologic and clinical resemblance of RAU to BD, differences in the count of blood leukocyte could be detected, therefore stressing a discrepancy related to its possible pathogenesis, which has previously been discussed by other authors [30].

In this study, a close relationship of the different groups of patients with ulcerations with rheumatologic diseases and immunodeficiency derangements could be noted, such as those patients having BD or OU; however, patients with RAU vaguely related to these comorbidities, contrary to previous observations [31,32]. It is important to consider that this study was performed in a tertiary care center where patients with complex systemic disease are referred; therefore, our results could be affected by a reference bias. Nonetheless, our results stress the need of the oral cavity inspection and close surveillance in this particular set of patients, considering the potential development of these ulcerations.

Some studies have suggested a significant relationship of RAU with the overall deficiency of vitamins and minerals [15,17,31,33-35]; however, these differences dilute when each vitamin or mineral is separately studied [9,36]. Our results could not confirm the association of ulcers and vitamin B₁₂ deficiency, perhaps because the statistical analysis was performed considering the sole deficiency of this vitamin, or because several factors related to RAU could have been present simultaneously in our patients. On the other hand, it may be possible that the importance

of the association of nutritional deficiencies to RAU may be less than previously attributed to their etiopathogenesis, or that all the related factors may only be considered as precipitants for the development of aphthae, as suggested by other authors [9,17,37].

Table 3: Etiologic factors related to the development of other recurrent ulcers.

Related factors	n	(%)
Trauma	32	(42.7)
Pemphigus vulgaris	8	(10.7)
Severe nutritional deficiencies	8	(10.7)
Hypersensitivity to drugs	7	(9.3)
Herpes simplex	7	(9.3)
Lupus erythematosus	6	(8)
Lichenoid reactions	2	(2.7)
Vasculopathy	2	(2.7)
Bacterial infection	1	(1.3)
Leukoplakia	1	(1.3)
Syphilis	1	(1.3)

Some other causes such as vigorous tooth-brushing, the use of a hard tooth brush, anesthesia infiltration, or dental treatment may frequently trigger the development of RAU [38]. In the group of OU observed in the current study, trauma was one of the main consistent related factors and not an isolated event, favoring the recurrence of ulcers; but at the same time eliciting a RAU misdiagnosis; consequently, trauma may be considered as a common cause when ruling out RAU.

In brief, mouth ulcers are common lesions that affect

Table 4: Clinical characteristics of oral ulcers in the studied groups.

Characteristics	Aphthae		Other ulcers		Behçet's disease	
	(n=56)		(n=75)		(n=10)	
	n	(%)	n	(%)	n	(%)
Type of aphthae						
Minor	16	(29)	10	(13.3)	1	(10)
Major	25	(45)	24	(32)	4	(40)
Herpetiform	1	(1.8)	-	-	-	-
Size & number of ulcers						
1-2 ulcers <1cm	19	(34)	30	(40)	3	(30)
More than 2 ulcers <1cm	10	(18)	13	(17.3)	2	(20)
1-2 ulcers >1cm	2	(1.8)	1	(1.3)	-	-
Symptomatology						
Asymptomatic	5	(9)	6	(8)	-	-
Slight	4	(7.1)	6	(8)	2	(20)
Moderate	4	(7.1)	2	(3)	-	-
Location						
Labial mucosa	18	(32.1)	19	(25.3)	4	(40)
Buccal/alveolar mucosa	12	(21.4)	27	(36)	4	(40)
Floor of the mouth	1	(1.8)	11	(15)	-	-
Ventral tongue	6	(11)	14	(19)	1	(10)
Soft palate/oropharynx	8	(14.3)	10	(13.3)	3	(30)
Dorsum of the tongue	6	(11)	7	(9.3)	1	(10)
Lateral borders of the tongue	4	(7.1)	17	(23)	3	(30)
Hard palate	-	-	9	(12)	-	-
Gingiva	-	-	14	(19)	-	-
Vermillion border/Cutaneous lip	-	-	2	(3)	-	-
Other mucosa						
No	18	(32.1)	6	(8)	-	-
Vaginal	1	(1.8)	2	(3)	3	(30)
Ocular	-	-	1	(1.3)	-	-
Previous treatment for ulcers						
Steroids	9	(16)	9	(12)	2	(20)
Antimycotic	4	(7.1)	13	(17.3)	5	(50)
Antacid	3	(5.3)	10	(13.3)	-	-
Poly-vitamin	7	(12.5)	-	-	-	-
Antibacterial	7	(3.5)	-	-	-	-
Antiviral	-	-	6	(8)	-	-
Folic acid	2	(12.5)	-	-	1	(10)
Cytotoxic	-	-	1	(1.3)	-	-
Psycotropic	-	-	1	(1.3)	-	-
Bronchodilator/antihistaminic	-	-	1	(1.3)	-	-

the swallowing process and directly interfere with the patient's quality of life and health. RAU diagnosis is based upon clinical features and may clinically be confounded with other types of ulcers. Despite many research efforts, their exact cause remains unknown. RAU have been attributed to diverse causes and they may be elicited by multiple factors, the above may hinder the research in these topics. It is possible that some of the features displayed by RAU may actually correspond to triggering clinical, inflammatory manifestations resulting in epithelial rupture of the oral mucosa as a response to different aggressive factors; therefore, it would be convenient to classify these types of ulcers, according to the related factors involved and not exclusively by the clinical and morphological features.

In this study, the recurrent ulcers found in the oral cavity showed important differences when analyzing variables such as blood leukocyte counts and the concomitant presence of systemic conditions, such as rheumatologic diseases. However, considering the retrospective design of this study, other factors probably involved in the development of RAU could not be evaluated.

Finally, in view of the variety and frequency of mouth ulcers, the difficulty upon establishing its diagnosis among physicians not acquainted to this type of lesions, and the small amount of studies performed by oral pathologists at hospital settings, more studies of this kind are warranted in order to expand the knowledge regarding the characterization and pathogenesis of the mouth ulcers, particularly RAU.

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