Recurrent Aphthous Stomatitis: Clinical Experience From a University Hospital in Brazil

Nathalia Targa Pinto, MD; Silvia Vanessa Lourenço, DDS; Marcello Menta Simonsen Nico, MD

PRACTICE **POINTS**

- The process that leads to the formation of aphthous ulcerations is always systemic, not local, even in the absence of a diagnosable systemic disease.
- Relapsing cases of aphthae should be treated with systemic medication.

To the Editor:
Recurrent aphthous stomatitis (RAS) is a mucocutaneous condition characterized by single or multiple, painful,[1,2] round ulcerations of variable sizes with a tendency for recurrence, most commonly located in nonkeratinized areas of the oral mucosa. Pathergy commonly is observed.[3] Although many authors consider the terms *RAS* and *aphtha* to be synonymous,[4,5] differentiating the clinical lesion (aphthous ulceration) from the disease (aphtha or RAS) can be useful, as several other diseases can at times manifest with similar ulcers (called *aphthoid lesions*), such as pemphigus vulgaris, mucous membrane pemphigoid, and erythema multiforme.[6]

It is estimated that approximately 20% of individuals worldwide have at least one episode of aphtha during their lifetime,[7] and it is considered the most common disease of the oral mucosa.[8,9] However, only patients presenting with severe acute outbreaks or frequent relapses typically seek medical treatment. Clinically, aphthous ulcers are classified as *aphtha minor* (small number of small lesions), *aphtha major* (large deep lesions that also can affect the minor salivary glands with intense necrosis, difficulty in healing, and mucosal scarring), and *aphtha herpetiformis* (innumerous tiny lesions that reappear in recurring outbreaks).[1-3] The term *complex aphthosis* was introduced in 1985[10] and is defined as recurrent oral and genital aphthous ulcerations or recurring multiple oral aphthous ulcers in the absence of systemic manifestations or Behçet disease[11,12]; however, complex aphthosis also has been reported as frequent episodes of ulcerations that may be associated with systemic diseases including Behçet disease.[13,14]

Currently, RAS is considered an immunologically mediated alteration in cutaneous mucosal reactivity with a multifactorial systemic cause. Underlying conditions such as Behçet disease, inflammatory bowel disease (IBD), iatrogenic immunosuppression (eg, following solid organ transplantation), AIDS, and cyclic neutropenia may or may not be detected.[11-13]

Our retrospective study explored the systemic nature of RAS. We reviewed patient records to evaluate underlying systemic conditions associated with the diagnosis of RAS and the use of oral medications in managing the disease. Medical records from the Department of Dermatology of the University of São Paulo, Brazil, from 2003 to 2017 were reviewed to identify patients with a diagnosis of RAS. Clinical classification of RAS—minor, major, or herpetiform—as well as the presence of aphthous lesions in other locations and the presence of other associated inflammatory cutaneous manifestations also were noted. Associated systemic diseases and treatments for RAS were recorded. Patients for whom the diagnosis of RAS was changed during follow-up were excluded.

From the Universidade de São Paulo, Brazil. Drs. Pinto and Nico are from the Department of Dermatology, Faculdade de Medicina, and Dr. Lourenço is from the Department of Pathology, Faculdade de Odontologia.
The authors report no conflict of interest.
Correspondence: Marcello Menta Simonsen Nico, MD, Departamento de Dermatologia, Faculdade de Medicina da Universidade de São Paulo, Brasil, R. Itapeva 500-3A. CEP-01332-000, São Paulo, Brasil (mentanico@hotmail.com).
Cutis. 2024 April;113(4):171-173. doi:10.12788/cutis.0992.

Because this was a retrospective analysis of medical records and without any patient risk, informed consent was not needed.

Medical records for 125 patients were reviewed; 63 were male (50.4%), and 62 were female (49.6%). The age at onset of symptoms, which ranged from a few months after birth to 74 years, was reported in only 92 (73.6%) patient medical records. Of these, 30 (32.6%) reported onset before 20 years of age, 39 (42.4%) between 20 and 39 years, 17 (18.5%) between 40 and 59 years, and 6 (6.5%) at 60 years or older. Morphologically, 72 (57.6%) had minor, 42 (33.6%) had major, and 11 (8.8%) had herpetiform aphthous ulcers. None of the patients presented with sporadic lesions; the disease was long-standing and persistent in all cases (complex aphthosis).

Regarding the location of the ulcers, 92 (73.6%) patients had lesions on the oral mucosa only. Some patients had lesions in more than one site in addition to the oral mucosa: 32 (25.6%) had aphthae in the genital/groin region and 4 (3.2%) presented with perianal/anal aphthae. Nineteen patients (19.2%) presented other cutaneous manifestations in addition to aphthae: 11 (45.8%) had folliculitis/pseudofolliculitis, and 8 (33.3%) had erythema nodosum (EN). Eight patients (33.3%) presented with uveitis, and 6 (25%) presented with concomitant arthralgia/arthritis. Fifty-four patients (43.2%) had confirmed or suspected associated disease: Behçet disease (21 [38.9%]), IBD (10 [18.5%]), solid organ transplantation (7 [13.0%])(kidney, 4 [57.1%]; heart, 2 [28.6%]; liver, 1 [14.3%]), HIV infection (6 [11.1%]), lymphoma (1 [1.9%]), aplastic anemia (1 [1.9%]), or myelodysplastic syndrome (1 [1.9%]). Ten patients (18.5%) presented with other diseases under investigation (eg, unidentified rheumatologic disease, unexplained neutropenia, undiagnosed immunodeficiencies, autoinflammatory syndromes, possible cyclic neutropenia).

Biopsies of the oral mucosa were performed in 31 patients. Histopathologic findings will be discussed in a future publication (unpublished data).

Five patients (4.0%) were lost to follow-up and did not receive treatment; 10 (8.0%) received only topical treatment (analgesics and/or corticosteroids). All 9 (7.2%) patients undergoing intralesional corticosteroid injections also were on a systemic treatment. One hundred ten (88.0%) patients were treated systemically—with colchicine (84/110 [76.4%]), thalidomide (43/110 [39.1%]), small pulses of oral corticosteroids (26 [23.6%]), dapsone (12/110 [10.9%]), or pentoxifylline (3 [2.7%]). Furthermore, in patients with associated diseases, treatment of the underlying condition was conducted when available, and follow-up was carried out in conjunction with the appropriate specialists. For treatment of the associated disease, patients received other medications such as methotrexate, azathioprine, cyclophosphamide, intravenous corticosteroid pulse, and immunobiologics.

The prevalence of RAS between sexes in our study population was similar (50.4% male; 49.6% female). Results from prior studies have been mixed; some reported a higher prevalence in females,[15-18] while others found no predilection for sex among patients diagnosed with RAS.[19,20] In our analysis, 75% of patients experienced symptoms of RAS before 40 years of age; in prior studies, up to 56% of patients experienced symptoms between the ages of 20 and 40 years.[21,22]

In our study, 26.4% of patients had extraoral aphthae. Genital lesions have been described as infrequent,[23] and lesions manifesting in other mucous membranes or on the skin are rare.[24] A study reported genital involvement in 8% to 13% of patients with oral aphtha.[25] We observed genital involvement in 25.6% of patients. Likewise, this higher value may be due to our study population of patients referred to our university hospital. In our study, 19.2% of patients presented with other inflammatory manifestations in addition to aphthous ulcerations (eg, folliculitis, EN, uveitis, arthritis). As dermatologists in a tertiary reference hospital, we actively look for such associations in every aphtha patient, which may not be the case in many nondermatologic oral care services.

In our study population, 43.2% of patients were diagnosed with or were under investigation for systemic diseases known to be associated with RAS. We found associations with Behçet disease most frequently, followed by IBD,[26] solid organ transplantation, and HIV. In this group of patients, the respective systemic disease was active or poorly controlled. In transplant recipients, aphtha major was the most common type, similar to other studies.[27] We observed no notable difference in the clinical picture of the oral ulcers in patients with a well-established systemic disease vs those without.

Most of our cases did not present findings other than aphtha, indicating that the intrinsic defect that predisposes to RAS is always systemic. Even mild and sporadic cases may be attributable to a systemic disorder of cutaneous-mucosal reactivity. The predisposition to RAS never originates in the oral cavity, hence the confusion caused and the uselessness of studies that relate aphthae to factors such as local food allergies, pH changes, or local infection with microorganisms.[5,28] The disease course (reducing the frequency of lesion appearance and accelerating the healing of extensive lesions) is only modified with systemic treatment, with local measures proving to be only moderately useful to relieve pain. We believe that RAS can in many ways be compared to EN and pyoderma gangrenosum (PG): some systemic conditions that predispose patients to EN and PG also may predispose them to RAS (eg, IBD, hematologic disorders). Similar to RAS, many cases of EN and PG are idiopathic. In addition, pathergy also occurs in PG.[11,13]

We were unable to observe or establish any predictive clinical element that could indicate a better or worse response to the prescribed treatments, which also has been noted by other authors.[3,4] Treatment of RAS is empiric, generally starting with drugs that are easier to prescribe and with fewer adverse effects, then progressing to more complex drugs when a good response is not obtained. Colchicine was the most commonly prescribed medication (76.4% [84/110]). It has been proposed by several authors[3,4] as a first-line systemic medication for the treatment of recurrent aphthae, as it has been shown to be effective and safe. The dosage ranged from 0.5 mg twice daily to 0.5 mg 4 times daily. Dapsone is an established drug for aphtha[29,30] and was used in 12 of our patients. The dosage used in our patients ranged from 50 to 100 mg/d. Adverse effects such as hemolytic anemia frequently are seen, and one of the patients in our study developed DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome in response to dapsone. In 7 cases, colchicine and dapsone were used together, which is believed to potentiate the therapeutic effects. This combination may be useful in patients for whom thalidomide cannot be used or those who have not improved with monotherapy.[29] Thalidomide is considered one of the most effective drugs for RAS.[30,31] Forty-three patients in our analysis were treated with thalidomide, usually as a first choice. The dosage ranged from 100 to 200 mg/d. It was mainly chosen in disabling pediatric cases, adult men with aphthous major, and women with no risk for pregnancy. Due to its potential adverse effects, thalidomide has been recommended when there is no response with other medications that are dose dependent; severe adverse effects such as thromboembolism and peripheral neuropathy are rare.[31] Oral corticosteroids were used in 26 patients, aiming at rapid improvement in very symptomatic cases; however, due to the potential for long-term adverse effects, in all cases they were prescribed in combination with another medication that was maintained after the corticosteroid was discontinued.

We highlight the systemic nature of RAS as well as its frequent association with systemic diseases and other correlated manifestations (pustules, EN, arthralgia). We also emphasize the importance of using oral medications to adequately control the disease and do not recommend topical medications aimed at treating local causes. Dermatologists should be consulted in managing severe cases of RAS.

REFERENCES

1. Buño IJ, Huff JC, Weston WL, et al. Elevated levels of interferon gamma, tumor necrosis factor alpha, interleukins 2, 4, and 5, but not interleukin 10, are present in recurrent aphthous stomatitis. *Arch Dermatol.* 1998;134:827-831.
2. Femiano F, Lanza A, Buonaiuto C, et al. Guidelines for diagnosis and management of aphthous stomatitis. *Pediatr Infect Dis J.* 2007; 26:728- 732.
3. Natah SS, Konttinen YT, Enattah NS, et al. Recurrent aphthous ulcers today: a review of the growing knowledge. *Int J Oral Maxillofac Surg.* 2004;33:221-234.
4. Zunt SL. Recurrent aphthous stomatitis. *Dermatol Clin.* 2003;21:33-39.
5. Jurge S, Kuffer R, Scully C, et al. Mucosal disease series. number VI. recurrent aphthous stomatitis. *Oral Dis.* 2006;12:1-21.
6. Chams-Davatchi C, Shizarpour M, Davatchi F, et al. Comparison of oral aphthae in Behçet's disease and idiopathic recurrent aphthous stomatitis. *Adv Exp Med Biol.* 2003;528:317-320.
7. Schemel-Suárez M, López-López J, Chimenos-Küstner E. Oral ulcers: differential diagnosis and treatment [in Spanish]. *Med Clin (Barc).* 2015;145:499-503.
8. Ślebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp (Warsz).* 2014;62:205-215.
9. Edgar NR, Saleh D, Miller RA. Recurrent aphthous stomatitis: a review. *J Clin Aesthet Dermatol.* 2017;10:26-36.
10. Jorizzo JL, Taylor RS, Schmalstieg FC, et al. Complex aphthosis: a forme fruste of Behçet's syndrome? *J Am Acad Dermatol.* 1985;13:80-84.
11. McCarty MA, Garton RA, Jorizzo JL. Complex aphthosis and Behçet's disease. *Dermatol Clin.* 2003;21:41-48.
12. Bulur I, Melrem O. Behçet disease: new aspects. *Clin Dermatol.* 2017;35:421-434.
13. Cui RZ, Rogers RS 3rd. Recurrent aphthous stomatitis. *Clin Dermatol.* 2016;34:475-481.
14. Femiano F, Lanza A, Buonaiuto C, et al. Guidelines for diagnosis and management of aphthous stomatitis. *Pediatr Infect Dis J.* 2007;26:728-732.
15. Ship II. Epidemiologic aspects of recurrent aphthous ulcerations. *Oral Surg Oral Med Oral Pathol.* 1972;33:400-406.
16. Ship JA. Recurrent aphthous stomatitis. an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1996;81:141-147.
17. Wilhelmsen NS, Weber R, Monteiro F, et al. Correlation between histocompatibility antigens and recurrent aphthous stomatitis in the Brazilian population. *Braz J Otorhinolaryngol.* 2009;75:426-431.
18. Ślebioda Z, Dorocka-Bobkowska B. Systemic and environmental risk factors for recurrent aphthous stomatitis in a Polish cohort of patients. *Postepy Dermatol Alergol.* 2019;36:196-201.
19. Ship JA, Chavez EM, Doerr PA, et al. Recurrent aphthous stomatitis. *Quintessence Int.* 2000;31:95-112.
20. Brocklehurst P, Tickle M, Glenny AM, et al. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). *Cochrane Database Syst Rev.* 2012;12:CD005411.
21. Belenguer-Guallar I, Jiménez-Soriano Y, Ariadna Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. a literature review. *J Clin Exp Dent.* 2014;6:E168-E174.
22. Bagán JV, Sanchis JM, Milián MA, et al. Recurrent aphthous stomatitis. a study of the clinical characteristics of lesions in 93 cases. *J Oral Pathol Med.* 1991;20:395-397.
23. Huppert JS, Gerber MA, Deitch HR, et al. Vulvar ulcers in young females: a manifestation of aphthosis. *J Pediatr Adolesc Gynecol.* 2006;19:195-204.
24. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. *J Oral Pathol Med.* 1989;18:21-27
25. Chapel TA. Origins of penile ulcerations. *Arch Androl.* 1979; 3: 351-357.
26. Lourenço SV, Hussein TP, Bologna SB, et al. Oral manifestations of inflammatory bowel disease: a review based on the observation of six cases. *J Eur Acad Dermatol Venereol.* 2010;24:204-207.
27. Nico MM, Brito AE, Martins LE, et al. Oral ulcers in an immunosuppressed 5-year-old boy. *Clin Exp Dermatol.* 2008;33:367-368.
28. Trakji B, Baroudi K, Kharma Y. The effect of dietary habits on the development of the recurrent aphthous stomatitis. *Niger Med J.* 2012;53:9-11.
29. Lynde CB, Bruce AJ, Rogers RS 3rd. Successful treatment of complex aphthosis with colchicine and dapsone. *Arch Dermatol.* 2009;145:273-276.
30. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol.* 2005(3 pt 1);52:500-508.
31. Hello M, Barbarot S, Bastuji-Garin S, et al. Use of thalidomide for severe recurrent aphthous stomatitis: a multicenter cohort analysis. *Medicine (Baltimore).* 2010;89:176-182.