Hematologic status in patients with recurrent aphthous stomatitis in Jordan

Samar Z. Burgan, MSc, PhD, *Faleh A. Sawair,* FDS RCS, PhD, *Zouhair O. Amarin,* MSc, FRCOG.

ABSTRACT

Objective: To determine the prevalence of hematinic deficiencies in patients with recurrent aphthous stomatitis.

Methods: The study took place in the Oral Medicine Clinic of the Jordan University Hospital in Amman, Jordan, between January 1993 and December 2000. We studied the hemoglobin, serum ferritin, vitamin B12 and folate levels in 143 patients with recurrent aphthous stomatitis. We compared the results with a control group of 143 age- and gender-matched patients with a range of other oral diseases.

Results: In recurrent aphthous stomatitis patients, 14% were anemic and 37.8% showed hematinic deficiencies; 16.8% showed low serum ferritin; 26.6% showed low serum vitamin B12 and 4.9% showed low serum folate. In the control group, 10.5% were anemic and 18.2% showed hematinic deficiencies; 9.8% showed low serum ferritin; 12.6% showed low serum vitamin B12 and none showed serum folate deficiency.

Conclusion: Patients with recurrent aphthous stomatitis have more hematinic deficiencies, particularly vitamin B12 deficiency, compared with controls. Correction of these hematinic deficiencies could help in the management of the disease.

Saudi Med J 2006; Vol. 27 (3): 381-384

Recurrent aphthous stomatitis (RAS) is a common oral mucosal disease occurring in up to 30% of the population.[1] It is one of the most painful oral lesions and can cause pain on eating, swallowing and speaking. It is characterized by recurring oral ulcers that usually begin in adolescence. Although the exact pathophysiology of RAS remains unclear and most patients with RAS are systemically well, various factors, such as genetics, immunological factors, allergic responses, microorganisms, local trauma, smoking, stress, hormonal factors and nutrition, can contribute to the pathogenesis of this clinical entity.[2-6] The uncertain nature of the pathogenesis is reflected in the variety of treatment modalities, none of which is uniformly successful. The prevalence of iron, folic acid and vitamin B12 deficiencies and their role in the development of RAS are not well known. Though some studies have denied an etiologic relationship between RAS and deficiencies of iron, folate or vitamin B12,[7] several studies have demonstrated a surprisingly high incidence of such hematinic deficiencies in patients with RAS.[8-11] Treating these deficiencies has been reported in preliminary[12,13] and controlled studies[14] to reduce or eliminate recurrences in most cases.

In this study, we aim to determine the frequency of anemia and deficiencies of iron, folate and vitamin B12 in Jordanian patients with RAS and to decide whether the level of hemoglobin on its own is adequate for screening patients with aphthae.

From the Department of Oral and Maxillofacial Surgery (Burgan, Sawair), Oral Medicine, Oral pathology and Periodontology, Faculty of Dentistry, University of Jordan and the Department of Obstetrics and Gynecology (Amarin), Faculty of Medicine, Jordan University of Science and Technology, Amman, *Jordan*.

Received 28th November 2005. Accepted for publication in final form 28th January 2006.

Address correspondence and reprint request to: Dr. Zouhair O. Amarin, PO Box 1572, Amman 11953, *Jordan*. Tel. +962 (79) 5225155. E-mail: zoamarin@hotmail.com

Table 1 - Types of recurrent aphthous stomatitis (RAS) in 143 patients (according to the criteria of Lehner[15])

Type of RAS	Male	Female	Total	(%)
Minor	55	61	116	(81.1)
Major	12	10	22	(15.4)
Herpetiform		5	5	(3.5)
Total	**67**	**76**	**143**	

Table 2 - Non-recurrent aphthous stomatitis (RAS) disease distribution in the control group

Diagnosis	Number of patients
Geogaphic tongue	9
Fissured tongue	2
Geographic and fissured tongue	10
Hairy tongue	19
Median rhomboid glossitis	4
Homogenous leukoplakia	14
Acquired angiodema	10
Benign tumor	8
Herpes labialis	2
Reticular lichen planus	32
Lip or cheek biting	11
Orofacial pain	22
Total	**143**

Methods. Consecutive patients referred to the Oral Medicine Clinic at the Jordan University Hospital, Amman, between January 1993 and December 2000 were included in this study. The RAS study group consisted of 143 patients with no other known systemic disease or any drug history. Patients with Behcet's disease and those with known hematologic or gastrointestinal disease were excluded. Their ages ranged from 17 - 67 years (median, 30 years). There were 76 female patients (median age, 32.5 years) and 67 male patients (median age, 30 years). The disease duration was 5 - 37 years (mean, 11 years). The diagnosis of RAS was based on history and clinical examination. The patients were classified as having minor aphthous ulcers, major aphthous ulcers, or herpetiform aphthous ulcers according to the criteria of Lehner[15] (**Table 1**).

The disease control group consisted of 143 patients with a range of oral conditions other than RAS that were not associated with hematinic deficiencies, who were age- and gender-matched to the study subjects (**Table 2**). Patients who had known systemic disease, or who were on medication were excluded from the study.

A full blood examination was carried out for all patients with RAS and the control subjects. Hemoglobin, serum ferritin, serum vitamin B12 and serum folate levels were determined for each patient. All subjects agreed to participate in the study and gave their consent after being informed in detail about the study. The laboratory values of 14-18 gr/dl (male) and 12-16 gr/dl (female) for hemoglobin, 17-230 ng/ml (male) and 14-150 ng/ml (female) for serum ferritin, >2.5 ng/ml for folate and

Table 3 - Hemoglobin, serum ferritin, serum folate and serum vitamin B12 levels in patients with recurrent aphthous stomatitis compared to control group

Test	Disease	Normal		Low		*p*-value
		No.	(%)	No.	(%)	
Hemoglobin	RAS	123	(86)	20	(14)	0.37
	Controls	128	(89.5)	15	(10.5)	
Ferritin	RAS	119	(83.2)	24	(16.8)	0.081
	Controls	129	(90.2)	14	(9.8)	
Folate	RAS	136	(95.1)	7	(4.9)	0.007
	Controls	143	(100)	0	(0)	
Vitamin B12	RAS	105	(73.4)	38	(26.6)	0.003
	Controls	125	(87.4)	18	(12.6)	
p-value of Chi-square test						

180-910 pg/ml for vitamin B12 were considered as normal values for Jordanian patients and formed the criteria for classification of patients. If a patient was found to have a low vitamin B12 and normal MCV, a repeat investigation of vitamin B12 (without any intervention) was conducted. Patients were included in the final analysis of the study if both test results were consistent. Patients with low vitamin B12 and raised MCV were referred to a gastroenterologist to rule out pernicious anemia before being included in the study.

The hemoglobin, serum ferritin, serum folate, and serum vitamin B12 levels were coded as normal or reduced and analyzed using a Statistical Package for Social Science version 10 database. Statistical analysis to compare patients with RAS and the disease control group was performed with Chi-square test. A p value of ≤0.05 was considered significant.

Results. The results for hemoglobin, serum ferritin, serum folate and serum vitamin B12 levels in patients with RAS compared to control group are shown in **Table 3**. Of the 143 patients with RAS, 20 patients (14%) were anemic compared to 15 patients of the 143 patients in the control group (10.5%). Although more patients with RAS showed reduced hemoglobin levels compared with the control group, the differences were far from being statistically significant. However, 7 patients showed low serum ferritin levels without anemia, 23 showed low serum vitamin B12 levels without anemia, 2 patients showed low serum ferritin and vitamin B12 levels without anemia and 4 patients showed low serum vitamin B12 and folate without anemia. Altogether, 54 patients with RAS (37.8%) showed low serum ferritin, folate or vitamin B12 compared with 26 (18.2%) of the control group. This difference was highly significant (p<0.001). Low levels of serum ferritin occurred in 16.8% of patients with RAS compared to 9.8% of patients with other oral lesions; the difference was close to being statistically significant (p=0.08). Seven patients (4.9%) with RAS while none of the control group showed low serum folate (p=0.007). More patients with RAS (26.6%) than the control group (12.6%) showed low serum vitamin B12 (p=0.003). Of the patients with RAS, 1.5% of the male patients were anemic compared with 25.3% of the females (p<0.001). In addition, low serum ferritin levels were detected in 6% of the male patients with RAS compared with 26.7% of the female patients (p=0.001). None of the male patients with RAS showed low serum folate levels, while 9.2% of the females were deficient to folate (p=0.01). No significant difference was found between males and females with RAS in terms of serum vitamin B12 levels. In patients with other lesions, no significant differences were found between males and females in the incidence of anemia, serum ferritin, folate and vitamin B12 levels. Fourteen patients with RAS had more than one deficiency; 2 patients had serum ferritin and folate deficiency, 7 patients had serum ferritin and vitamin B12 deficiency and 5 had serum folate and vitamin B12 deficiency. Six patients of the control group had both low serum ferritin and vitamin B12 levels.

Discussion. It has long been thought that iron, folate and vitamin B12 deficiencies play an important role in RAS, but some controversy does exist. Wray et al[8] reported hematinic deficiencies to affect up to 21% of adult patients with RAS, and when they replaced the deficient element, 59% of the patients showed resolution of RAS and 28% showed significant improvement. However, other studies have shown that patients with RAS and controls had comparable serum iron, folate or vitamin B12.[7,9,16-18] In addition, replacement therapy had not always been effective; studies had shown that most patients with a proven vitamin B12 or folate deficiency improved rapidly on replacement therapy, while those with iron deficiency had shown a less remarkable response.[14,18] However, patients with RAS may demonstrate low serum iron secondary to chronic disease but have normal serum ferritin levels. Since such patients do not have true primary iron-deficiency anemia, they would not be likely to benefit from iron replacement therapy.[19] Therefore; this may explain the inconsistent response to replacement therapy in previously mentioned studies that had relied on serum iron levels and total iron binding capacity to direct therapy.[14]

Rogers et al[13] studied 102 patients with RAS in USA and found that only 5.9% were anemic; however, 39.2% of the patients showed hematinic deficiencies. Similarly, Challacombe et al[16] studied 193 patients with RAS in London and found that 7.3% were anemic and 30.6% showed hematinic deficiencies. No previous studies had been conducted in Jordan to evaluate the prevalence of anemia and hematinic deficiencies in patients with RAS. In the present study, 14% of the patients with RAS and a comparable proportion of the control group (10.5%) were anemic. However; in keeping with studies conducted in USA and Britain,[13,16] 37.8% of Jordanian patients with RAS showed hematinic deficiencies. Therefore, determination of the level of hemoglobin alone is not adequate in investigating patients with RAS.

In this study, vitamin B12 deficiency was the most prevalent (26.6%), followed by iron deficiency (16.8%) and folate deficiency (4.9%). However, serum folate

is not an accurate marker of folate status and values can vary widely dependent on the patients' recent diet. The best assay is corrected whole blood folate since most folate is within red cells, but our hospital's laboratory was not prepared to offer corrected whole blood folate routinely. In the case of serum ferritin, the difference between patients with RAS and the control group was not statistically significant and the number of patients with RAS who had low serum folate was small to draw any conclusions. In addition, low serum ferritin and folate levels were significantly more common in females than males. Therefore, hematinic deficiencies, particularly of vitamin B12, which is independent of the patients' gender, may be an important contributing factor in the etiopathogenesis of RAS. However, controlled therapeutic trials are required to find the frequency which vitamin B12 deficiency actually predisposes to RAS and whether vitamin B12 replacement in such patients would lead to significant improvement. Results of such studies may determine whether screening utilizing a complete blood count and measurement of serum ferritin, folate and vitamin B12 levels are important in the evaluation and management of patients with RAS.

References

1. Miller MF, Ship II. A retrospective study of the prevalence and incidence of recurrent aphthous ulcers in a professional population, 1958-1971. ***Oral Surg Oral Med Oral Pathol*** 1977; 43: 532-537.
2. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. ***J Oral Pathol Med*** 1989; 18: 21-27.
3. Nolan A, Lamey PJ, Milligan KA, Forsyth A. Recurrent aphthous ulceration and food sensitivity. ***J Oral Pathol Med*** 1991; 20: 473-475.
4. Vincent SD, Lilly GE. Clinical, historic, and therapeutic features of aphthous stomatitis. Literature review and open clinical trial employing steroids. ***Oral Surg Oral Med Oral Pathol*** 1992; 74: 79-86.
5. Porter SR, Kingsmill V, Scully C. Audit of diagnosis and investigations in patients with recurrent aphthous stomatitis. ***Oral Surg Oral Med Oral Pathol*** 1993; 76: 449-452.
6. Fischman SL. Oral ulcerations. ***Semin Dermatol*** 1994; 13: 74-77.
7. Olson JA, Feinberg I, Silverman S Jr, Abrams D, Greenspan JS. Serum vitamin B12, folate, and iron levels in recurrent aphthous ulceration. ***Oral Surg Oral Med Oral Pathol*** 1982; 54: 517-520.
8. Wray D, Ferguson MM, Hutcheon WA, Dagg JH. Nutritional deficiencies in recurrent aphthae. ***J Oral Pathol*** 1978; 7: 418-423.
9. Challacombe SJ, Scully C, Keevil B, Lehner T. Serum ferritin in recurrent oral ulceration. ***J Oral Pathol*** 1983; 12: 290-299.
10. Field EA, Rotter E, Speechley JA, Tyldesley WR. Clinical and haematological assessment of children with recurrent aphthous ulceration. ***Br Dent J*** 1987 11; 163: 19-22.
11. Porter SR, Scully C, Flint S. Hematologic status in recurrent aphthous stomatitis compared with other oral disease. ***Oral Surg Oral Med Oral Pathol*** 1988; 66: 41-44.
12. Porter S, Flint S, Scully C, Keith O. Recurrent aphthous stomatitis: the efficacy of replacement therapy in patients with underlying hematinic deficiencies. ***Ann Dent*** 1992; 51: 14-16.
13. Rogers RS 3rd, Hutton KP. Screening for hematinic deficiencies in patients with recurrent aphthous stomatitis. ***Australas J Dermatol*** 1986; 27: 98-103.
14. Wray D, Ferguson MM, Mason DK, Hutcheon AW, Dagg JH. Recurrent aphthae: treatment with vitamin B12, folic acid, and iron. ***Br Med J*** 1975; 2: 490-493.
15. Lehner T. Autoimmunity in oral diseases, with special reference to recurrent oral ulceration. ***Proc R Soc Med*** 1968; 61: 515.
16. Challacombe SJ, Barkhan P, Lehner T. Haematological features and differentiation of recurrent oral ulceration. ***Br J Oral Surg*** 1977; 15: 37-48.
17. Piskin S, Sayan C, Durukan N, Senol M. Serum iron, ferritin, folic acid, and vitamin B12 levels in recurrent aphthous stomatitis. ***J Eur Acad Dermatol Venereol*** 2002; 16: 66-67.
18. Rennie JS, Reade PC, Hay KD, Scully C. Recurrent aphthous stomatitis. ***Br Dent J*** 1985; 159: 361-367.
19. Woo SB, Sonis ST. Recurrent aphthous ulcers: a review of diagnosis and treatment. ***J Am Dent Assoc*** 1996; 127: 1202-1213.