HEMATOLOGIC ABNORMALITIES IN RECURRENT ORAL ULCERATION

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Abstract. The aim of this study was to analyse the hematologic status in patients with recurrent oral ulceration (ROU) . Twenty-three patients with ROU and 19 control subjects were examined consecutively for hematological abnormalities including serum folate, red cell folate and vitamin B_{12} levels. Their complete blood counts, hemoglobin typing, serum and red cell folate and serum vitamin B_{12} levels were studied. Low red cell folate levels were found in 11 out of 23 patients (47.83%) with ROU. They were defined as having folate deficiency (n=5), folate deficient erythropoiesis (n=1), and folate depletion (n=5). The serum and red cell folate levels in the control group were within normal range. There was a statistically significant low red cell folate in the ROU compared to the control group (p=0.000).The serum vitamin B_{12} levels were within normal range in both ROU and control groups. Hemoglobin, hematocrit and mean corpuscular hemoglobin concentrations were in the normal range in both groups and none had anemia or macrocytosis.

INTRODUCTION

Some studies have suggested that hematological disorders can affect the oral mucosa and cause recurrent oral ulceration (ROU) (Tyldesley, 1983; Field *et al*, 1995). The significance of hematological abnormalities in oral pathology is still unclear and controversy remains about the need for full hematological assessment in patients with oral ulceration (Challacombe *et al*, 1977). It has been suggested that a deficiency of iron, vitamin B_{12}, or folic acid might play a role in the pathogenesis of ROU (Wray *et al*, 1975), although this hypothesis has been rejected by others (Porter and Scully, 1991; Vincent and Lilly, 1992), so there is a divergence of opinion about whether a full blood examination, including serum folate, red cell folate and serum vitamin B_{12} determination, should be mandatory.

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The purpose of our study was to determine the hematological status of a series of patients with ROU including the levels of red cell folate, serum folate and vitamin B_{12}, and to investigate relationships between the underlying causes of ROU.

PATIENTS AND METHODS

Twenty-three patients with ROU who had been referred to the Oral Medicine Department, Faculty of Dentistry, Chulalongkorn University, between 1996 and 2001 were enrolled in the study. Twenty-three ROU patients (18 females, 5 males) with histories of oral ulceration recurring within 3 months were studied. All cases had more than one site of the lesion and had been diagnosed as minor type (n=20), major type (n=2) or herpetiform type (n=1). The types of lesions, the duration of symptoms, medication, gastrointestinal disorders and more broadly systemic diseases were recorded. Additionally, 19 healthy volunteers (13 females, 6 males) were included as the control group: they had no oral lesions or systemic diseases. Dental caries and gingivitis

were found in some of the healthy volunteers. Ages ranged from 21 to 60 years (mean±SD = 34.84±10.79) in the control group, 22 to 58 years (mean±SD = 34.04±10.21) in the ROU group.

Consent was obtained from all patients and controls before drawing venous blood. Samples were taken between 10.00 and 12.00 hours in order to minimize the effects of diurnal variation. Of a total of 10 ml whole blood, 3 ml was collected into a EDTA blood tube and the remainder in a plain tube for clotted blood. Blood samples were quickly transported to the laboratory in a cool container.

Hematological investigations carried out on all patients and control subjects comprised a full blood count and determination of hemoglobin (Hb), folate and vitamin B_{12} status. Serum folate, red cell folate and serum B_{12} levels were determined by competition binding radioassay. The complete blood count was performed by standard method using a Coulter Counter and hemoglobin typing was analysed by electrophoresis. Anemia was defined as a hematocrit of less than 39% for males and less than 36% for females. Macrocytosis was defined as a mean corpuscular volume (MCV) > 100 fl, normocytosis by MCV of 80-96 fl and microcytosis by MCV < 80 fl (Dacie and Lewis, 1995). A red cell folate level < 100 ng/ml was defined as folate deficiency, 100-120 ng/ml as folate deficient erythropoiesis and 120-160 ng/ml as folate depletion (Herbert, 1987). A serum vitamin B_{12} level < 150 pg/ml was defined as low (Herbert, 1994).

RESULTS

The characteristics of twenty-three patients with ROU, duration of disease at presentation and associated conditions are shown in Table 1.The duration of disease varied from 4-288 months (mean=84.35 ± SD 78.48). Systemic conditions were found in 16 of 23 cases (69.6%) while 5 patients were taking medications. Three patients who were taking dilantin, estrogen and diclofenac, respectively, showed low red cell

Table 1
Sex and age of patients, duration of disease at presentation and associated conditions.

Group	N	Sex		Age (yrs) mean ± SD (range)	Duration of disease (months) mean ± SD (range)	Associated conditions[a] (number of cases)	
		F	M			Systemic conditions	Medications
ROU	23	18	5	34.04 ± 10.21 (22-58)	84.35 ± 78.48 (4-288)	Gastrointestinal disorders (7) HbE trait (3) β-thalassemia traits (2) Turner's syndrome (1) Atopic (1) Migraine (1) Epilepsy (1) Rheumatoid arthritis (1) Osteoarthritis (1)	Estrogen (1) Antihistamines (1) Ergotamine tartrate (1) Diclofenac (1) Dilantin (1) Phenylbutazone (1)
Control	19	13	6	34.84 ± 10.79 (21-60)	-	-	-

[a]Some patients had more than one systemic condition and were taking more than one medication.

Table 2
The means and ranges of serum folate, red cell folate and serum vitamin B_{12} levels in patients with ROU compared with the control subjects.

Group	No.	Serum folate[a] (ng/ml)	Red cell folate (ng/ml)	Vitamin B_{12} (pg/ml)
ROU	23	9.35	238.00	557.9
		(2.30-32.58)	(85-1,085)	(208-1,458)
Control	19	13.74	309.00	514.72
		(5.37-32.49)	(202-629)	(321-997)

[a]The normal ranges in the Thai control group are serum folate 5-24 ng/ml, red cell folate 221-1,113 ng/ml and serum vitamin B_{12} 211-911 pg/ml (Value from Department of Tropical Radioisotope, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand).

folate levels. The means and ranges of serum folate, red cell folate and serum vitamin B_{12} levels in patients with ROU and the control subjects are shown in Table 2. The mean serum and red cell folate levels in patients with ROU were lower than those of the control subjects. Table 3 shows the hematological data in patients with ROU compared with the control subjects The serum vitamin B_{12} levels were within normal range in both groups. Low red cell folate levels were found in 11 out of 23 patients with ROU (47.83%); of these, 5 were defined as folate deficiency, 1 as folate deficient erythropoiesis and 5 as folate depletion. There was a statistically significant difference in red cell folate level between ROU and the control groups (p=0.000). Two ROU patients were found to have low MCVs, defined as microcytosis. HbE trait was found in 1 case each with Turner's syndrome, peptic ulcer and no systemic diseases, however, their hemoglobin level, hematocrit and mean corpuscular hemoglobin concentration were in the normal ranges. The serum vitamin B_{12} levels in both ROU and control groups were normal. Although the red cell folate levels were below 100 ng/ml, none of them had anemia or macrocytosis.

DISCUSSION

In our study, the finding that 11 of 23 cases with ROU showed low red cell folate differed from some other published results (Porter *et al*, 1988). That report found a minority of patients with deficiencies of folate. Our study found that low red cell folate levels were associated with gastrointestinal disorders such as gastritis, peptic ulceration and appendectomy, medications, HbE trait, no systemic diseases or stress, which are not similar to the results of another previous study (Tyldesley, 1983). However, the frequency of oral lesions such as angular cheilitis and aphthous ulceration showed no correlation with inflammatory bowel diseases (Lisciandrano *et al*, 1996). We suggest routine hematologic screening should be performed in all ROU patients, especially in cases with no response to medications. Interestingly, three cases with no systemic diseases that showed low red cell folate had oral ulcerations for a long period. Such cases may have primary immunologic abnormalities (Landesberg *et al*, 1990). One of 3 cases with HbE trait showed a low MCV whereas the others were normal. Five patients in this study were taking medication, only 2 of these patients were taking drugs known to reduce folate. Two cases were taking medications such as oral estrogen or dilantin which have been implicated as a cause of low folate levels (Duxbury, 1990; Harper *et al*, 1994). Moreover, low red cell folate in a patient who was taking diclofenac was also found in this study.

Table 3
Hematological abnormalities in patients with ROU and the control subjects.

	No	Folate deficiency (<100 ng/ml)	Folate deficient erythropoiesis (100-120 ng/ml)	Folate depletion (120-160 ng/ml)	Vitamin B_{12} (<150 pg/ml)	Hb (<11 g/dl)	MCV (<80 fl)	MCV (>100 fl)
ROU	23	5	1	5	-	-	2	-
Control	19	-	-	-	-	-	-	-

One case with a history of epilepsy, who had been treated with dilantin for more than 15 years had red cell folate deficiency (85 ng/ml); after treatment with a topical steroid [fluocinolone acetonide 0.1% in orabase, (FAO)] and folic acid (5 mg twice daily) the lesions showed improvement. She was referred to her physician for changing drug treatment of epilepsy but she dropped out from the Oral Medicine Clinic, thus being lost to long-term follow-up.

In the case of a patient with Turner's syndrome, association of the HbE trait was revealed by the hematological assessment. She had been taking microganon and atenolol for more than 10 years. A burning sensation and oral ulceration were found in this case, however management with folic acid 5 mg twice daily reduced signs and symptoms. Folic acid administration was reduced and then stopped when there were normal mucosa and no other symptoms . This case showed a good response to management during 4 years follow-up.

Various side effects of drugs have been described in the oral cavity, including oral ulcerations. The diagnosis is usually difficult, particularly with patients receiving multiple drug therapy. Non-steroidal anti-inflammatory drugs which are commonly prescribed in rheumatology, such as diclofenac, flurbiprofen, indomethacin and naproxen can cause oral ulcers (Madinier *et al*, 2000). One case with osteoarthritis who was regularly taking diclofenac showed low red cell folate (148 ng/ml). Recurrent oral ulceration appeared in his oral cavity for more than 60 months before he entered to the Oral Medicine clinic program. Treatment such case with FAO and folic acid together with a recommendation to his physician that diclofenac be changed to other drugs resulted in good healing. Discontinuing non-steroidal anti-inflammatory drugs, and starting a palliative plan have been reported to help resolve oral ulceration (Siegel and Balciunas, 1991). Thus, elimination of the drugs that can cause oral ulceration is important for treatment and management of ROU.

Stress and psychological illness have been

proposed to initiate some episodes of recurrent oral stomatitis (Ship *et al*, 1961; Miller *et al*, 1977). One case with stress had a history of oral ulcerations developed during a period of hard work. This case showed clinical improvement after treatment with folic acid and FAO. During the treatment period, recommendation that the patient undertake relaxation exercises has been found to be useful for management.

Although the relationship between ROU and hematological deficiencies is still controversial, the present study confirms that folate deficiency in Thai patients can be associated with ROU. The underlying causes associated with oral manifestations should also be sought for correction. Drugs known to reduce folate levels interfere with DNA synthesis by a common mechanism. (Wray and Dagg, 1990). Folic acid is necessary for all body cells, especially to enhance the regeneration and healing of the oral epithelium in response to damage. Accurate hematologic assessment is considered important in the diagnosis and management of this deficiency. That our findings are somewhat different from previous reports might be because our ROU cases were referred and hence we tended to receive many of the worst cases. It is appropriate to undertake full hematologic investigations including folate levels in patients with oral lesions who had no response to any medications (Thongprasom *et al*, 2001). Because only a single blood sample was obtained from each subject, longitudinal studies of large groups and long-term observation are required for better clarification.

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