FOLATE AND VITAMIN B_{12} LEVELS IN PATIENTS WITH ORAL LICHEN PLANUS, STOMATITIS OR GLOSSITIS

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Abstract. Forty-one patients with oral lesions and symptoms were enrolled in the study. Their ages ranged from 16 to 79 years with a mean age of 48.5 years. They were divided into two groups. Group I consisted of 25 patients with oral lichen planus and group II consisted of 16 patients with stomatitis or glossitis. Their complete blood counts, hemoglobin typing, serum and red cell folate, and serum vitamin B_{12} levels were studied. The results revealed low red cell folate levels in 11 out of 25 patients (44%) in group I and 9 out of 16 patients (56%) in group II. The serum vitamin B_{12} levels were within normal range in both groups. They were defined as having folate deficiency (n = 10), folate deficient erythropoiesis (n = 3) and folate depletion (n = 7). None of them had anemia nor macrocytes. Therefore, folate levels should be investigated in patients with oral lesions and symptoms especially those with risk factors of age, poor nutrition or systemic diseases. When suspected, daily folic acid supplements should be given.

INTRODUCTION

It has been recognized that hematological disorders can affect the oral mucosa as in glossitis, stomatitis, recurrent aphthous ulceration and angular cheilitis (Tyldesley, 1983; Field *et al*, 1995). Furthermore, in one study, the prevalence of hematological abnormalities in the erosive oral lichen planus group was significantly greater than in the non-erosive group (Challacombe,1986). The oral changes occur in the absence of any abnormalities in the complete blood count (Olson *et al*, 1982). It is difficult to establish whether the oral lesions are directly due to the underlying disease or reflect a hematologic deficiency. Also, there is some divergence of opinion as to whether a complete hematologic testing, is mandatory in each case (Challacombe *et al*, 1977). The purpose of this study was to perform the complete hematological testing in patients with oral lichen planus, stomatitis or glossitis.

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PATIENTS AND METHODS

Forty-one patients with oral lesions and symptoms referred to the Oral Medicine Department, Faculty of Dentistry, Chulalongkorn University from 1996-1999, were enrolled in the study. The duration of symptoms, type of lesions, medication and systemic diseases were recorded. The patients were divided into two groups. Group I consisted of 25 patients (21 females, 4 males) with erosive or atrophic oral lichen planus who were diagnosed by clinical manifestations and confirmed by histopathological studies (Walsh *et al*, 1990; Eversole, 1994; Scully *et al*, 1998). Group II consisted of 16 patients (11 females, 5 males) with stomatitis or glossitis. Their primary complaints included sore mouth, discomfort in the tongue without lesions and erythematous or atrophic lingual mucosa. Candida infection had been excluded. Additionally, 17 healthy volunteers (12 females, 5 males) were included as the control group. They had no oral lesions upon clinical examination or complaints, apart from dental caries or gingivitis. The ages ranged from 16 to 79 years (mean ± SD = 48 ± 17) in group I, 21 to 74 years (mean ± SD = 49 ± 13.5) in group II and 21 to 60 years (mean

± SD = 35.4 ± 11.3) in the control group.

Consent was obtained from all patients and control subjects before drawing venous blood. Samples were taken between 10 and 12 am in an attempt to minimized any effects of diurnal variation.

Laboratory investigation

The laboratory investigation included a complete blood count, hemoglobin typing and determining folate and vitamin B_{12} levels. The complete blood count was performed by standard method using Coulter Counter and the hemoglobin typing was analysed by electrophoresis. Serum folate, red cell folate and serum vitamin B_{12} levels were determined by competition binding radioassays.

Anemia was defined as a hematocrit of less than 39% for males and less than 36% for females. The macrocyte was defined as a mean corpuscular volume (MCV) above 100 fl, normocyte of MCV 80-96 fl and microcyte of MCV less than 80 fl (Dacie and Lewis, 1995). A red cell folate level below 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 less than 150 pg/ml was defined as low (Herbert, 1994).

Statistics

The chi-square test or Fisher's exact test was used to compare the groups. A p value of less than 0.05 was considered significant.

RESULTS

The means and ranges of serum folate, red cell folate and serum vitamin B_{12} levels among the subjects are shown in Table 1. The red cell folate in patients with oral lichen planus and stomatitis/glossitis were lower than those of the control subjects and of the normal ranges ($p<0.001$). The serum vitamin B_{12} levels were within normal ranges. Low red cell folate levels were determined in 11 out of 25 patients (44%) in group I and 9 out of 16 patients (56%) in group II (Table 2). Although their red cell folate levels were below 100 ng/ml, none of them had anemia or macrocytes.

In addition, five patients in group I and two patients in group II were found to have low MCVs, defined as microcytes. Only two of the patients in group I revealed homozygous hemoglobin E and heterozygous HbE from hemoglobin typing, one each. The rest had normal hemoglobin typing which excluded the β-thalassemia and hemoglobin E traits. However, the α-thalassemia traits could not be

Table 1
The means and ranges of serum folate, red cell folate and serum vitamin B_{12} levels in patients with oral lichen planus, stomatitis or glossitis compared with the control subjects.

	Number	Serum folate[a] (ng/ml)	Red cell folate[a] (ng/ml)	Vitamin B_{12}[a] (pg/ml)
Group I	25	10.7	245.9	516.5
Oral lichen planus		(1.3-48.9)	(30-1,361)	(199-1,775)
Group II	16	14.3	172.7	629.5
Stomatitis/glosssitis		(3.3-30.6)	(55-463)	(208-1,806)
Control subjects	17	14.4	319.8	486.3
		(5.4-32.5)	(214-629)	(321-646)

[a]The normal ranges in the Thai control group were 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 Radioisotopes, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand).

Table 2
The folate status determined by red cell folate levels among patients with oral lichen planus, stomatitis or glossitis.

	Folate deficiency <100 ng/ml	Folate deficient erythropoiesis 100-120 ng/ml	Folate depletion 120-160 ng/ml	Normal >160 ng/ml
Group I: Oral lichen planus (n=25)	5	1	5	14
Group II: Stomatitis/glossitis (n=16)	5	2	2	7

excluded. Moreover, two females had low hematocrits of 28% and 34%, and iron deficiency was suspected. Furthermore, the investigation for serum iron and total iron binding capacity (TIBC) were normal in these cases.

The mean ± SD durations of symptoms in group I and II were 36.3 ± 43 (range 1-175) and 41 ± 43.3 (range 1-120) months, respectively.There was no statistically significant difference between group I and group II or between patients with normal and low folate levels. Also, associated systemic diseases were found in 7 out of 25 patients (28%) in group I and 5 out of 16 patients (31%) in group II, which included hypertension (n=4), peptic ulcer (n=3) , diabetes mellitus (n=3), hyperlipidemia (n=3), gastritis (n=1). Two patients had an additional disease. Their medication did not interfere with folate metabolism except those taking antacid for peptic ulcer or gastritis (n=3), or estrogen for menopause (n=2) as shown in Table 3. As a result, three out of five patients had low red cell folate levels defined as folate deficiency (n=1) or folate deficient erythropoiesis (n=2). None of them had anemia or macrocytes.

DISCUSSION

In this study, only a single blood sample was obtained from each subject. Although some patients had low serum folate levels of less than 3 ng/ml, they were not diagnosed with folate deficiency. On the contrary, a low serum folate level represented a negative folate balance at the time of blood sample was drawn. The red cell folate levels are more specific than the serum folate levels. Therefore, red cell folate levels of less than 160, 120 and 100 ng/ml are used for determining the status of folate depletion, deficient erythropoiesis and deficiency, respectively. Even though the patients with red cell folate less than 100 ng/ml had no anemia, folate deficiency anemia could not be excluded. The more specific diagnostic method of giving a low dose of folate 100-200 mg/day and observing the ensuing reticulocytosis and rise in hemoglobin levels, was not included in this study.

Since the prevalence of α-thalassemia traits among the Thai population is 20-30% (Wasi, 1981), they are suspected in subjects with low MCVs. Their MCVs range from 65 to 75 fl with normal hematocrits.

The recommended daily allowances (RDAs) of folate intake is 3 μg of total per kg body weight. This is about 180 μg/day for women and 200 μg/day for men (Brody, 1994). Folate is essential for maintaining oral mucosa. Inadequate folate intake is the most common cause of folate deficiency. A low folate intake for three to six months is able to produce a folate deficient status. Additionally, the folate in food is partially destroyed during cooking. Elderly persons are more likely to have low levels of serum and red cell folate due to insufficient intake of fresh vegetable, fruits and fruit juice (Varadi and Elvis, 1966). In addition, oral estrogen have been implicated as a cause of low folate levels (Harper *et al*,

Table 3
The descriptive data and laboratory findings of five patients taking medications that interfered with folate metabolism.

No.	Sex	Age	Diagnosis	Duration of symptoms (months)	Systemic diseases	Medications	Hematocrit (%)	MCV (fl)	Serum folate[a] (ng/ml)	Red cell folate[a] (ng/ml)	Vitamin B_{12} [a] (pg/ml)
1	F	57	OLP	117	[b]	estrogen	40	98.5	3.6	109	405
2	F	24	OLP	2	peptic ulcer	antacid	39	96.8	3.84	393	320
3	F	49	OLP	36	[b]	estrogen	40	93.7	17.43	163	559
4	F	74	glossitis	5	gastritis	antacid	44	94.4	11.74	103	343
5	M	48	glossitis	12	peptic ulcer	antacid	44	92.5	10.48	58.91	208

[a]The normal ranges in the Thai control group were: 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 Radioisotopes, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand).
OLP = Oral lichen planus.
[b]menopause

1994). Antacid, which alters the pH in the stomach and intestines, may be another contributing factor in folate absorption. Normally, optimal folate absorption takes place in the jejunum at a pH of 5.5 (Russel *et al*, 1988).

Folate levels should be investigated in patients with oral lesions and symptoms, especially those with risk factors of age, poor nutrition or systemic diseases. They may have low folate levels in the absence of any abnormalities in the complete blood count. When suspected, folic acid supplements should be given. Two tablets of folic acid 5 mg per day for one month are sufficient to restore the folate in the liver and red cells. However, if risk factors still exist, daily folic acid supplements are suggested.

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