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 B₁₂ levels. Their complete blood counts, hemoglobin typing, serum and red cell folate and serum vitamin B₁₂ 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 B₁₂ 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 B₁₂, 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 B₁₂ determination, should be mandatory.

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 B₁₂, 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 B₁₂ status. Serum folate, red cell folate and serum B₁₂ 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 B₁₂ 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
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.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Serum folate (ng/ml)</th>
<th>Red cell folate (ng/ml)</th>
<th>Vitamin $B_{12}$ (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROU</td>
<td>23</td>
<td>9.35 (2.30-32.58)</td>
<td>238.00 (85-1,085)</td>
<td>557.9 (208-1,458)</td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>13.74 (5.37-32.49)</td>
<td>309.00 (202-629)</td>
<td>514.72 (321-997)</td>
</tr>
</tbody>
</table>

*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).
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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