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Original Article

Anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody positivity in 588 patients with oral lichen planus

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Abstract *Background/purpose:* Our previous study found that 21.9 %, 13.6 %, 7.1 %, 0.3 %, and 14.8 % of 352 oral lichen planus (OLP) patients have anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. This study mainly evaluated the anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity in a large group of 588 OLP patients.
Materials and methods: The blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 588 OLP patients were measured and compared with the corresponding levels in 588 age- and sex-matched healthy control subjects.
Results: We found that 148 (25.2 %), 99 (16.8 %), 60 (10.2 %), 7 (1.2 %), 124 (21.1 %), and 139 (23.6 %) OLP patients had blood Hb, serum iron, vitamin B12, and folic acid deficiencies,

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hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 588 OLP patients had significantly higher frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects (all *P*-values <0.001 except $P = 0.023$ for folic acid deficiency). Of 148 anemic OLP patients, 68 had normocytic anemia, 32 had iron deficiency anemia, 19 had thalassemia trait-induced anemia, 17 had pernicious anemia, 7 had macrocytic anemia other than pernicious anemia, and 5 had microcytic anemia other than iron deficiency anemia and thalassemia trait-induced anemia.

Conclusion: OLP patients have significantly higher frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than healthy control subjects.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease that occurs more frequently in middle-aged and elderly female patients and affects 0.2–3% of the population.[1–3] OLP more commonly involves the buccal mucosa, tongue, and gingiva. The OLP lesions usually have a bilateral and symmetric distribution on the oral mucosa.[3] Clinically, 6 types of OLP, including reticular, papular, plaque-like, erosive/atrophic, ulcerative, and bullous types, can be identified.[2,3]

A previous study has revealed that OLP involves both antigen-specific and non-specific mechanisms. Antigen-specific mechanisms encompass antigen presentation by basal keratinocytes and antigen-specific keratinocyte killing by $CD8^+$ cytotoxic T lymphocytes. Non-specific mechanisms involve mast cell degranulation and the activation of matrix metalloproteinases in OLP lesions.[1] In OLP lesions, mast cell-T-cell interactions facilitate the mast cells to release cytokines, chemokines, and matrix metalloproteinases that in turn promote T-cell activation, migration, proliferation, and differentiation.[4] From a histological perspective, OLP displays features such as the liquefaction degeneration of basal epithelial cells and the presence of mononuclear cells within both the intra-epithelial and subepithelial regions, with a predominant $CD8^+$ cell population. $CD4^+$ cells are primarily located in the deep lamina propria.[5] Additionally, an increase in histocompatibility leukocyte antigen (HLA)-DR-positive $CD3^+$ cells, observed in both local lesional tissues and peripheral blood lymphocytes, further indicates the activation of T-cells in OLP.[6,7] These findings collectively support the notion that OLP is an inflammatory disease primarily mediated by T-lymphocytes.

Because OLP was considered to be a T-lymphocyte-mediated immunological disorder, only few studies evaluated the hematological abnormalities and nutritional deficiencies in OLP patients.[8–10] Nevertheless, deficiencies of iron,[8] vitamin B12,[8] and folate[8–10] have been reported in a portion of OLP patients. Our previous study found that 21.9 %, 13.6 %, 7.1 %, 0.3 %, and 14.8 % of 352 OLP patients have anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively.[11] This study mainly evaluated the anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity in a large group of 588 OLP patients.

Materials and methods

Participants

This study included 588 OLP patients (110 men and 478 women, age range 20–88 years, mean 55.8 ± 14.1 years). For each OLP patient, one age- (±2 years of each patient's age) and sex-matched healthy control subject was selected. Thus, 588 (110 men and 478 women, age range 20–89 years, mean 56.0 ± 14.1 years) age- and sex-matched healthy control subjects were selected and included in this study. All the patients and control subjects were seen consecutively, diagnosed, and treated in the Department of Dentistry, National Taiwan University Hospital (NTUH) from July 2007 to June 2023. The 588 OLP patients were selected according to the following criteria: (i) presentation of characteristic clinical features such as radiating grayish-white Wickham striae, papules, plaques, either individually or in combination, and erosion or ulceration on the oral mucosa; (ii) a bilateral and symmetric distribution of OLP lesions on the oral mucosa. For 25 patients with an uncertain clinical OLP diagnosis, an incisional biopsy of the typical oral mucosal lesion was conducted. Confirmation of the histopathological diagnosis of OLP occurred when biopsy specimens displayed the hallmark characteristics of the condition, including hyperkeratosis or parakeratosis, a slightly acanthotic epithelium with liquefaction degeneration of basal epithelial cells, a prominent band-like lymphocytic infiltrate in the lamina propria, and the absence of epithelial dysplasia.[3,11–14] However, OLP patients who had a habit of betel quid chewing, autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, pemphigus vulgaris, and cicatricial pemphigoid), inflammatory diseases, malignancy, or recent surgery were excluded from the study. Furthermore, OLP patients with serum creatinine concentrations indicating renal dysfunction (i.e., men >131 μmol/L; women >115 μmol/L) and those who had a history of stroke, heavy alcohol use, or suffered from

diseases of the liver, kidney, or coronary arteries were also excluded.[11–14] The healthy control subjects displayed either dental caries or mild periodontal diseases and had no oral mucosal or systemic illnesses. None of the OLP patients had been prescribed any medication for OLP for a minimum of three months prior to their participation in the study.

The blood samples were drawn from 588 OLP patients and 588 healthy control subjects for the measurement of complete blood count, serum iron, vitamin B12, folic acid, and homocysteine concentrations, and the serum GPCA positivity. All OLP patients and healthy control subjects signed the informed consent forms before entering the study. This study was reviewed and approved by the Institutional Review Board at the NTUH (202402086RINC).

Determination of blood hemoglobin, iron, vitamin B12, folic acid, and homocysteine concentrations

The complete blood count and serum iron, vitamin B12, folic acid, and homocysteine concentrations were determined by the routine tests performed in the Department of Laboratory Medicine, NTUH.[11–37]

Determination of serum gastric parietal cell antibody level

The serum GPCA level was detected by the indirect immunofluorescence technique with rat stomach as a substrate as described previously.[11–37] Sera were scored as positive when they produced fluorescence at a dilution of 10-fold or more.

Statistical analysis

Comparisons of the mean corpuscular volume (MCV) and mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels between 588 OLP patients and 588 healthy control subjects were performed by Student's *t*-test. The differences in frequencies of microcytosis (MCV $<$80 fL),[30–32] macrocytosis (MCV $\geq$100 fL),[33–37] blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity between 588 OLP patients and 588 healthy control subjects were compared by chi-square test. The result was considered to be significant if the *P*-value was less than 0.05.

Results

The MCV, mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels in 588 OLP patients and 588 healthy control subjects are shown in Table 1. Because men usually had higher blood levels of Hb and iron than women, these two mean levels were calculated separately for men and women. We found that 588 OLP patients had significantly lower MCV, mean blood Hb (for men and women), serum iron (for women only), vitamin B12, and folic acid levels, and a significantly higher mean serum homocysteine level than 588 healthy control subjects (all *P*-values $<$0.001, Table 1). However, no significant difference in the mean serum iron level was found between 110 male OLP patients and 110 male healthy control subjects (Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV $<$80 fL,[30–32] macrocytosis of erythrocyte was defined as having MCV $\geq$100 fL,[33–37] and men with Hb $<$ 13 g/dL and women with Hb $<$ 12 g/dL were defined as having Hb deficiency or anemia.[38] Furthermore, patients with the serum iron level $<$60 μg/dL,[39,40] the serum vitamin B12 level $<$200 pg/mL,[41] or the folic acid level $<$4 ng/mL[42] were defined as having serum iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level $>$12.0 μM (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations, Table 1) were defined as having hyperhomocysteinemia. By the above-mentioned definitions, 13.3 %, 6.1 %, 25.2 %, 16.8 %, 10.2 %, 1.2 %, 21.1 %, and 23.6 % of 588 OLP patients were diagnosed as having microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 588 OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than

Table 1 Comparisons of mean corpuscular volume (MCV) and mean blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels between 588 oral lichen planus (OLP) patients and 588 healthy control subjects.

	Mean ± SD		[a]*P*-value (Student's *t*-test)
	OLP patients (n = 588)	Healthy control subjects (n = 588)	
MCV (fL)	88.4 ± 8.5	90.4 ± 3.8	<0.001
Hb (g/dL)			
Men	14.6 ± 1.5 (n = 110)	15.2 ± 0.8 (n = 110)	<0.001
Women	12.7 ± 1.3 (n = 478)	13.5 ± 0.8 (n = 478)	<0.001
Iron (μg/dL)			
Men	99.1 ± 36.8 (n = 110)	103.6 ± 27.9 (n = 110)	0.308
Women	82.8 ± 30.3 (n = 478)	96.7 ± 27.4 (n = 478)	<0.001
Vitamin B12 (pg/dL)	572.9 ± 258.8	682.6 ± 231.7	<0.001
Folic acid (ng/dL)	12.7 ± 6.2	14.7 ± 5.8	<0.001
Homocysteine (μM)	9.3 ± 3.6	8.2 ± 1.9	<0.001

[a] Comparisons of means of parameters between 588 OLP patients and 588 healthy control subjects by Student's *t*-test.

Table 2 Comparisons of frequencies of microcytosis (mean corpuscular volume or MCV <80 fL), macrocytosis (MCV ≥100 fL), blood hemoglobin and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity between 588 oral lichen planus (OLP) patients and 588 healthy control subjects.

Factor	Patient number (%)		
	OLP patients (n = 588)	Healthy control subjects (n = 588)	*P*-value[a] (Chi-square test)
Microcytosis (MCV <80 fL)	78 (13.3)	0 (0.0)	<0.001
Macrocytosis (MCV ≥100 fL)	36 (6.1)	0 (0.0)	<0.001
Hemoglobin deficiency (Men <13 g/dL, Women <12 g/dL)	148 (25.2)	0 (0.0)	<0.001
Iron deficiency (<60 μg/dL)	99 (16.8)	0 (0.0)	<0.001
Vitamin B12 deficiency (<200 pg/dL)	60 (10.2)	0 (0.0)	<0.001
Folic acid deficiency (<4 ng/dL)	7 (1.2)	0 (0.0)	0.023
Hyperhomocysteinemia (>12.0 μM)	124 (21.1)	10 (1.7)	<0.001
GPCA positivity	139 (23.6)	10 (1.7)	<0.001

[a] Comparisons of frequencies of parameters between 588 OLP patients and 588 healthy control subjects by chi-square test.

588 healthy control subjects (all *P*-values <0.001 except $P = 0.023$ for folic acid deficiency, Table 2).

In this study, 148 OLP patients had anemia (defined as having an Hb concentration <13 g/dL for men and <12 g/dL for women).[38] Of these 148 anemic OLP patients, 17 (11.5 %) had pernicious anemia (PA, defined as having anemia, an MCV ≥100 fL, a serum vitamin B12 level <200 pg/mL, and the presence of serum GPCA positivity),[33–37,43] 7 (4.7 %) had macrocytic anemia (defined as having anemia and an MCV ≥100 fL) other than PA,[33–37,43] 68 (46.0 %) had normocytic anemia (defined as having anemia and an MCV between 80 fL and 99.9 fL),[44–47] 32 (21.6 %) had iron deficiency anemia (IDA, defined as having anemia, an MCV <80 fL, and a serum iron level <60 μg/dL),[38–40] and 19 (12.8 %) had thalassemia trait-induced anemia (defined as having anemia, a red blood cell count >5.0 M/μL, an MCV <74 fL, and a Mentzer index (MCV/RBC) < 13),[48] and 5 (3.4 %) had microcytic anemia (defined as having anemia and an MCV <80 fL)[30–32,40] other than IDA and thalassemia trait-induced anemia. These findings indicate that by the strict WHO criteria the normocytic anemia (46.0 %), IDA (21.6 %), and thalassemia trait-induced anemia (12.8 %) are the three most common types of anemia in our 148 anemic OLP patients.

Discussion

This study found that 25.2 %, 16.8 %, 10.2 %, 1.2 %, 21.1 %, and 23.6 % of 588 OLP patients had anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. These findings were comparable to the results of our previous study that showed 21.9 %, 13.6 %, 7.1 %, 0.3 %, and 14.8 % of 352 OLP patients have anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively.[11] Moreover, both studies demonstrated that OLP patients had significantly higher frequencies of blood Hb and serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than healthy control subjects.[11] The results of these two studies indicate that approximately 22–25 %, 14–17 %, and 15–21 % OLP patient may have anemia, serum iron deficiency, and heperhomocysteinemia, respectively.[11] In addition, approximately 24–26 % of OLP patients may have the serum GPCA positivity.[12] The high frequencies of the serum GPCA positivity in these two relatively large groups of our OLP patients also confirms that OLP may be an autoimmune oral mucosal disease.[12]

The hematological abnormalities and nutritional deficiencies were infrequently investigated in OLP patients.[8–10] Challacombe[8] studied the hematological abnormalities in 103 OLP patients and demonstrated anemia and lower serum iron, folate, and vitamin B12 levels in 9 (8.7 %), 13 (12.6 %), 3 (2.9 %), and 2 (1.9 %) OLP patients, respectively. Thongprasom et al.[9] discovered the low red cell folate level in 11 (44 %) of 25 OLP patients. However, the serum vitamin B12 levels of OLP patients were within the normal range.[9] Jolly and Nobile[10] found folic acid deficiency (<3 ng/mL) in 5 of 34 OLP patients. Our previous study found that 77 (21.9 %), 48 (13.6 %), 25 (7.1 %) and 1 (0.3 %) OLP patients had blood Hb and serum iron, vitamin B12 and folic acid deficiencies, respectively.[11] This study also showed that 148 (25.2 %), 99 (16.8 %), 60 (10.2 %) and 7 (1.2 %) OLP patients had blood Hb and serum iron, vitamin B12, and folic acid deficiencies, respectively. The results of the previous study and present study indicate that there is a small group of OLP patients definitely having anemia or hematinic deficiencies.[11] Therefore, supplementation of hematinics or multiple B vitamins may be beneficial to this specific group of OLP patients. Actually, Jolly and Nobile[10] observed good and some improvement in 20 and 9 of 41 vitamin-deficient OLP patients treated with multiple vitamin supplements, respectively. However, complete remission of the OLP lesions was not seen within two months of commencing vitamin therapy.[10] This finding suggests that although the frequency of hematinic deficiency is significantly higher in OLP patients than in healthy control subjects, hematinic deficiency is probably not the main etiology causing the OLP.[10]

This study showed anemia in 148 (25.2 %) of our 588 OLP patients. The normocytic anemia (46.0 %, 68 patients) was the most common type of anemia in our 148 anemic OLP patients (Table 3). Although the normocytic anemia was associated with chronic diseases, inflammatory diseases, infections, bone marrow hypoplasia, decreased production

Table 3 Anemia types, serum iron, vitamin B12, and folic acid deficiencies, and gastric parietal cell antibody (GPCA) positivity in 148 anemic oral lichen planus (OLP) patients.

Anemia type	Patient number (%)					
	Anemic OLP patient number (%)	Mean corpuscular volume (fL)	Iron deficiency (<60 μg/dL)	Vitamin B12 deficiency (<200 pg/mL)	Folic acid deficiency (<4 ng/mL)	GPCA positivity
OLP patients (n = 588)						
Pernicious anemia	17 (11.5)	≥100	2 (11.8)	17 (100.0)	0 (0.0)	17 (100.0)
Other macrocytic anemia	7 (4.7)	≥100	0 (0.0)	5 (71.4)	0 (0.0)	2 (28.6)
Normocytic anemia	68 (46.0)	80–99.9	30 (44.1)	12 (17.7)	2 (2.9)	12 (17.7)
Iron deficiency anemia	32 (21.6)	<80	32 (100.0)	6 (18.8)	0 (0.0)	9 (28.1)
Thalassemia trait-induced anemia	19 (12.8)	<74	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Other microcytic anemia	5 (3.4)	<80	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Total	148 (100.0)		64 (43.2)	41 (27.7)	2 (1.4)	41 (27.7)

of erythropoietin or a poor response to erythropoietin, hemolytic disorders, mild but persistent blood loss from gastrointestinal tract, and cytokine-induced suppression of erythropoiesis,[44–47] serum iron, vitamin B12, and folic acid deficiencies were observed in 44.1 %, 17.7 %, and 2.9 % of 68 OLP patients with normocytic anemia in this study, respectively (Table 3). Iron deficiency results in microcytic erythrocytes[30–32,38–40] and vitamin B12 and folic acid deficiencies cause macrocytic erythrocytes.[33–37] If the anemic patients have concomitant deficiencies of iron, vitamin B12, and folic acid, they may have anemia with normal-sized erythrocytes (normocytic anemia).[44–47]

IDA was found in 32 (21.6 %) of 148 anemic OLP patients in this study (Table 3). In addition to having iron deficiency, 6 (18.8 %) and none of the 32 IDA/OLP patients had serum vitamin B12 and folic acid deficiencies, respectively (Table 3). Besides, a decreased intake of iron, chronic blood loss, and a reduced absorption of iron in OLP patients with gastrointestinal diseases were also possible causes of IDA.[38–40] In this study, 9 (28.1 %) of 32 IDA/OLP patient had serum GPCA positivity. Therefore, GPCA-induced hypochlorhydria was also a minor factor leading to malabsorption of iron from gastric and duodenal mucosae and subsequent iron deficiency.[39]

This study identified PA in 17 (11.5 %) of 148 anemic OLP patients. All of these 17 PA patients had vitamin B12 deficiency, hyperhomocysteinemia, and serum GPCA positivity. Moreover, 2 (11.8 %) PA/OLP patients also had serum iron deficiency and none had folic acid deficiency (Table 3). Patients with GPCA positivity had destruction of gastric parietal cells by an autoimmune mechanism, resulting in intrinsic factor deficiency, lack of absorption of vitamin B12 from terminal ileum, and finally vitamin B12 deficiency.[35,36] Our previous study showed that 6 (7.8 %) of 77 anemic OLP patients had PA.[11] In addition, our previous study and this study also discovered that 3 (7.3 %) of 41 GPCA-positive erosive OLP patients and 17 (12.2 %) of 139 GPCA-positive OLP patients had PA.[14] These findings indicate that only 7.3 %–12.2 % of GPCA-positive OLP patients have PA.

Thalassemia trait-induced anemia was demonstrated in 19 (12.8 %) of our 148 anemic OLP patients (Table 3). Of these 19 OLP patients with thalassemia trait-induced anemia, none had serum iron, vitamin B12, and folic acid deficiencies, indicating that the Hb deficiency in our 19 OLP patients with thalassemia trait-induced anemia is not associated with hematinic (e.g., iron, vitamin B12, and folic acid) deficiencies, but is predominantly due to gene mutation resulting in insufficient production of either the α-globin or β-globin chains of the Hb molecule.[48]

Homocysteine is generated as a byproduct of methionine metabolism.[49] Both vitamin B12 and folic acid serve as coenzymes in the process of converting homocysteine into methionine.[50] Furthermore, vitamin B6 facilitates the conversion of homocysteine into cysteine.[50] Consequently, individuals with deficiencies in vitamin B12, folic acid, and/or vitamin B6 may exhibit elevated levels of homocysteine, a condition known as hyperhomocysteinemia.[49,50] A previous study has shown that a supplementation with folic acid and vitamins B12 and B6 can reduce blood homocysteine levels.[51] Our previous studies also demonstrated that supplementations with vitamin BC capsules plus corresponding deficient vitamin B12 and/or folic acid can reduce the abnormally high serum homocysteine level to significantly lower levels in patients with either atrophic glossitis or burning mouth syndrome.[52,53] In this study, vitamin B12 deficiency, folic acid deficiency, and hyperhomocysteinemia were observed in 10.2 %, 1.2 %, and 21.1 % of our 588 OLP patients, respectively. We suggest that hyperhomocysteinemia in our OLP patients are at least partially due to deficiencies of vitamin B12 and folic acid in our OLP patients, although the vitamin B12 and folic acid deficiencies are only minor factors. Elevated levels of homocysteine (hyperhomocysteinemia) can be attributed to various factors. These include enzyme and cofactor dysfunctions involved in homocysteine biosynthesis, excessive methionine consumption, specific medical conditions such as chronic renal failure, hypothyroidism, pernicious or sickle cell anemia, and the presence of malignant tumors in the breast, ovary, and pancreas. Additionally, certain medications, including cholestyramine, metformin, methotrexate, nicotinic acid, and fibric acid derivatives, may also contribute to hyperhomocysteinemia as a side effect.[54] However, further studies are needed to elucidate the exact etiologies that cause hyperhomocysteinemia in our OLP patients.

This study demonstrated that 13.3 %, 6.1 %, 25.2 %, 16.8 %, 10.2 %, 1.2 %, 21.1 %, and 23.6 % of 588 OLP patients had microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies,

hyperhomocysteinemia, and serum GPCA positivity, respectively. We also found significantly higher frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in our 588 OLP patients than in 588 healthy control subjects. These findings indicate that there are significantly higher frequencies of anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in OLP patients than in healthy control subjects.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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None.

References

1. Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rew Oral Biol Med* 2002;13:350—65.
2. Scully C, Beyli M, Ferreiro MC, et al. Update on oral lichen planus: etiopathogenesis and management. *Crit Rev Oral Biol Med* 1998;9:86—122.
3. Chiang CP, Chang JYF, Wang YP, Wu YH, Lu SY, Sun A. Oral lichen planus — differential diagnoses, serum autoantibodies, hematinic deficiencies, and management. *J Formos Med Assoc* 2018;117:756—65.
4. Zhao ZZ, Savage NW, Sugerman PB, Walsh LJ. Mast cell/T cell interactions in oral lichen planus. *J Oral Pathol Med* 2002;31:189—95.
5. Khan A, Farah CS, Savage NM, Walsh LJ, Harbrow DJ, Sugerman PB. Th1 cytokines in oral lichen planus. *J Oral Pathol Med* 2003;32:77—83.
6. Hirota J, Osaki T, Tatemoto Y. Immunohistochemical staining of infiltrates in oral lichen planus. *Pathol Res Pract* 1990;186:625—32.
7. Yamamoto T, Yoneda K, Ueta E, Osaki T. Cellular immunosuppression in oral lichen planus. *J Oral Pathol Med* 1990;19:464—70.
8. Challacombe SJ. Haematological abnormalities in oral lichen planus, candidiasis, leukoplakia and non-specific stomatitis. *Int J Oral Maxillofac Surg* 1986;15:72—80.
9. Thongprasom K, Youngnak P, Aneksuk V. Folate and vitamin B12 levels in patients with oral lichen planus, stomatitis or glossitis. *Southeast Asian J Trop Med Publ Health* 2001;32:643—7.
10. Jolly M, Nobile S. Vitamin status of patients with oral lichen planus. *Aust Dent J* 1977;22:446—50.
11. Chen HM, Wang YP, Chang JYF, Wu YC, Cheng SJ, Sun A. Significant association of deficiencies of hemoglobin, iron, folic acid, and vitamin B12 and high homocysteine level with oral lichen planus. *J Formos Med Assoc* 2015;114:124—9.
12. Chang JYF, Chiang CP, Hsiao CK, Sun A. Significantly higher frequencies of presence of serum autoantibodies in Chinese patients with oral lichen planus. *J Oral Pathol Med* 2009;38:48—54.
13. Chang JYF, Chen IC, Wang YP, Wu YH, Chen HM, Sun A. Anemia and hematinic deficiencies in gastric parietal cell antibody-positive and antibody-negative erosive oral lichen planus patients with thyroid antibody positivity. *J Formos Med Assoc* 2016;115:1004—11.
14. Chang JYF, Wang YP, Wu YH, Su YX, Tu YK, Sun A. Hematinic deficiencies and anemia statuses in anti-gastric parietal cell antibody-positive or all autoantibodies-negative erosive oral lichen planus patients. *J Formos Med Assoc* 2018;117:227—34.
15. Chiang CP, Wu YH, Wu YC, Chang JYF, Wang YP, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody positivity in 884 patients with burning mouth syndrome. *J Formos Med Assoc* 2020;119:813—20.
16. Chiang CP, Wu YC, Wu YH, Chang JYF, Wang YP, Sun A. Gastric parietal cell and thyroid autoantibody in patients with burning mouth syndrome. *J Formos Med Assoc* 2020;119:1758—63.
17. Chiang ML, Jin YT, Chiang CP, Wu YH, Chang JYF, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with vitamin B12 deficiency. *J Dent Sci* 2020;15:34—41.
18. Chiang ML, Chiang CP, Sun A. Anemia, hematinic deficiencies, and gastric parietal cell antibody positivity in burning mouth syndrome patients with or without hyperhomocysteinemia. *J Dent Sci* 2020;15:214—21.
19. Jin YT, Wu YH, Wu YC, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, and hyperhomocysteinemia in serum gastric parietal cell antibody-positive burning mouth syndrome patients without serum thyroid autoantibodies. *J Dent Sci* 2021;16:1110—6.
20. Wu YH, Jin YT, Wu YC, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with normocytosis. *J Dent Sci* 2022;17:35—41.
21. Jin YT, Wu YH, Wu YC, Chang JYF, Chiang CP, Sun A. Higher gastric parietal cell antibody titer significantly increases the frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia in patients with burning mouth syndrome. *J Dent Sci* 2022;17:57—62.
22. Jin YT, Wu YC, Wu YH, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, and hyperhomocysteinemia in burning mouth syndrome patients with thyroglobulin antibody/thyroid microsomal antibody positivity but without gastric parietal cell antibody positivity. *J Dent Sci* 2022;17:106—12.
23. Wu YH, Jin YT, Wu YC, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, and hyperhomocysteinemia in male and female burning mouth syndrome patients. *J Dent Sci* 2022;17:935—41.
24. Wu YH, Wu YC, Chang JYF, Lang MJ, Chiang CP, Sun A. Anemia, hematinic deficiencies, and hyperhomocysteinemia in younger and older burning mouth syndrome patients. *J Dent Sci* 2022;17:1144—50.
25. Wu YH, Wu YC, Chang JYF, Lee YP, Chiang CP, Sun A. Significantly higher frequencies of macrocytosis, anemia, serum vitamin B12 and folic acid deficiencies, and hyperhomocysteinemia in male than in female atrophic glossitis patients. *J Dent Sci* 2022;17:1371—7.
26. Wu YH, Wu YC, Chang JYF, Lee YP, Chiang CP, Sun A. Significantly lower mean serum vitamin B12 and folic acid levels and a significantly higher frequency of serum iron deficiency in younger than in older atrophic glossitis patients. *J Dent Sci* 2022;17:1487—93.
27. Wu YH, Lee YP, Chang JYF, Wang YP, Chiang CP, Sun A. Higher frequencies of anemia, hematinic deficiencies, and gastric parietal cell antibody positivity in vitamin B12-deficient Taiwanese male oral submucous fibrosis patients. *J Dent Sci* 2023;18:367—73.
28. Wu YH, Lee YP, Chang JYF, Wang YP, Chiang CP, Sun A. High frequencies of vitamin B12 and folic acid deficiencies and hyperhomocysteinemia in Taiwanese male patients with oral submucous fibrosis. *J Dent Sci* 2023;18:407—13.

29. Wu YH, Lee YP, Chang JYF, Wang YP, Chiang CP, Sun A. Higher frequencies of anemia, vitamin B12 deficiency, and gastric parietal cell antibody positivity in folic acid-deficient Taiwanese male oral submucous fibrosis patients. *J Dent Sci* 2023;18:801—7.
30. Chiang CP, Chang JYF, Wang YP, Wu YC, Wu YH, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody positivity in atrophic glossitis patients with or without microcytosis. *J Formos Med Assoc* 2019;118:1401—7.
31. Jin YT, Wu YC, Wu YH, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with or without microcytosis. *J Dent Sci* 2021;16:608—13.
32. Lin HP, Wu YH, Wang YP, Wu YC, Chang JYF, Sun A. Anemia and hematinic deficiencies in gastric parietal cell antibody-positive and —negative oral mucosal disease patients with microcytosis. *J Formos Med Assoc* 2017;116:613—9.
33. Jin YT, Wu YH, Wu YC, Chang JYF, Chiang CP, Sun A. Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with macrocytosis. *J Dent Sci* 2021;16:1133—9.
34. Chiang CP, Wu YH, Chang JYF, Wang YP, Wu YC, Sun A. Hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in atrophic glossitis patients with macrocytosis. *J Formos Med Assoc* 2019;118:1515—21.
35. Sun A, Wang YP, Lin HP, Jia JS, Chiang CP. Do all the patients with gastric parietal cell antibodies have pernicious anemia? *Oral Dis* 2013;19:381—6.
36. Sun A, Chang JYF, Wang YP, Cheng SJ, Chen HM, Chiang CP. Do all the patients with vitamin B12 deficiency have pernicious anemia? *J Oral Pathol Med* 2016;45:23—7.
37. Chang JYF, Wang YP, Wu YC, Cheng SJ, Chen HM, Sun A. Hematinic deficiencies and pernicious anemia in oral mucosal disease patients with macrocytosis. *J Formos Med Assoc* 2015;114:736—41.
38. WHO/UNICEF/UNU. *Iron deficiency anemia assessment, prevention, and control: a guide for programme managers*. Geneva, Switzerland: World Health Organization, 2001.
39. Wu YC, Wang YP, Chang JYF, Cheng SJ, Chen HM, Sun A. Oral manifestations and blood profile in patients with iron deficiency anemia. *J Formos Med Assoc* 2014;113:83—7.
40. Shine JW. Microcytic anemia. *Am Fam Physician* 1997;55:2455—62.
41. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr* 2007;85:193—200.
42. de Benoist B. Conclusions of a WHO technical consultation on folate and vitamin B12 deficiencies. *Food Nutr Bull* 2008;29(suppl):S238—44.
43. Lahner E, Annibale B. Pernicious anemia: new insights from a gastroenterological point of view. *World J Gastroenterol* 2009;15:5121—8.
44. Brill JR, Baumgardner DJ. Normocytic anemia. *Am Fam Physician* 2000;62:2255—63.
45. Koury MJ, Rhodes M. How to approach chronic anemia. *Hematology Am Soc Hematol Educ Program* 2012;2012:183—90.
46. Koury MJ. Abnormal erythropoiesis and the pathophysiology of chronic anemia. *Blood Rev* 2014;28:49—66.
47. Means Jr RT. Pathogenesis of the anemia of chronic disease: a cytokine-mediated anemia. *Stem Cell* 1995;13:32—7.
48. Wang YP, Chang JYF, Wu YC, Cheng SJ, Chen HM, Sun A. Oral manifestations and blood profile in patients with thalassemia trait. *J Formos Med Assoc* 2013;112:761—5.
49. Spence JD. Homocysteine-lowering therapy: a role in stroke prevention? *Lancet Neurol* 2007;6:830—8.
50. Chanarin I, Deacon R, Lumb M, Perry J. Cobalamin-folate interrelations. *Blood Rev* 1989;3:211—5.
51. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567—77.
52. Sun A, Wang YP, Lin HP, Chen HM, Cheng SJ, Chiang CP. Significant reduction of homocysteine level with multiple B vitamins in atrophic glossitis patients. *Oral Dis* 2013;19:519—24.
53. Sun A, Lin HP, Wang YP, Chen HM, Cheng SJ, Chiang CP. Significant reduction of serum homocysteine level and oral symptoms after different vitamin supplement treatments in patients with burning mouth syndrome. *J Oral Pathol Med* 2013;42:474—9.
54. Kim J, Kim H, Roh H, Kwon Y. Causes of hyperhomocysteinemia and its pathological significance. *Arch Pharm Res (Seoul)* 2018;41:372—83.