Journal of Dental Sciences 20 (2025) 1877–1884

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Original Article

Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in oral lichen planus patients with or without microcytosis

Yi-Pang Lee [a,b†], Ying-Tai Jin [c,d†], Julia Yu-Fong Chang [e,f,g], Yi-Ping Wang [e,f,g], Andy Sun [e**], Chun-Pin Chiang [a,b,e,f*]

[a] *Department of Dentistry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan*
[b] *Institute of Oral Medicine and Materials, College of Medicine, Tzu Chi University, Hualien, Taiwan*
[c] *Department of Pathology, Taiwan Adventist Hospital, Taipei, Taiwan*
[d] *Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[e] *Department of Dentistry, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[f] *Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, Taipei, Taiwan*
[g] *Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan*

Received 9 May 2025; Final revision received 10 May 2025
Available online 22 May 2025

KEYWORDS
Oral lichen planus;
Anemia;
Iron;
Hyperhomocysteinemia;
Microcytosis

Abstract *Background/purpose:* Microcytosis is defined as having mean corpuscular volume (MCV) < 80 fL. This study evaluated whether 78 oral lichen planus (OLP) patients with microcytosis (microcytosis/OLP patients) and 510 OLP patients without microcytosis (non-microcytosis/OLP patients) had higher frequencies of anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity than 588 healthy control subjects.
Materials and methods: Complete blood count and serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 healthy control subjects were measured and compared.
Results: We found that 71.8 %, 46.2 %, 10.3 %, 0.0 %, 18.0 %, and 20.5 % of 78 microcytosis/OLP

* Corresponding author. Department of Dentistry, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, and Institute of Oral Medicine and Materials, College of Medicine, Tzu Chi University, No. 707, Section 3, Chung-Yang Road, Hualien 970, Taiwan.
** Corresponding author. Department of Dentistry, National Taiwan University Hospital, No. 1, Chang-Te Street, Taipei 10048, Taiwan.
E-mail addresses: andysun7702@yahoo.com.tw (A. Sun), cpchiang@ntu.edu.tw (C.-P. Chiang).
† These two authors contributed equally to this work.

https://doi.org/10.1016/j.jds.2025.05.009

patients and 18.0 %, 12.4 %, 10.2 %, 1.4 %, 21.6 %, and 24.1 % of 510 non-microcytosis/OLP patients had blood hemoglobin, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Both 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients had significantly higher frequencies of blood hemoglobin, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects (all *P*-values <0.001). Moreover, 78 microcytosis/OLP patients had significantly higher frequencies of blood hemoglobin and serum iron deficiencies than 510 non-microcytosis/OLP patients.

Conclusion: We conclude that our 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients have significantly higher frequencies of anemia, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects. Moreover, 78 microcytosis/OLP patients also have significantly higher frequencies of blood hemoglobin and serum iron deficiencies than 510 non-microcytosis/OLP patients.

Introduction

Microcytosis is defined as having mean corpuscular volume (MCV) $<$ 80 fL.[1–4] Microcytosis is caused by deficiency of hemoglobin (Hb) structure components including heme (consisted of iron and protoporphyrine IX), α-globin, and β-globin.[1–4] Iron deficiency may cause iron deficiency anemia (IDA),[5] defects in the synthesis of the heme group may result in sideroblastic anemia,[4] and lack of synthesis of α-globin or β-globin may lead to thalassemia trait-induced anemia.[6] Because α-globin and β-globin are the two major structural proteins of the Hb and are responsible for maintaining the volume of an erythrocyte, patients with the lack of synthesis of either α-globin or β-globin (such as α-thalassemia or β-thalassemia, respectively) usually have the erythrocytes with the size being smaller than the erythrocytes in patients with IDA.[6] Therefore, it is interesting to know whether oral lichen planus (OLP) patients with microcytosis (so-called microcytosis/OLP patients) might have significantly higher frequencies of anemia and serum iron deficiency than OLP patients without microcytosis (so-called non-microcytosis/OLP patients).

Our previous study found that 78 (13.3 %), 148 (25.2 %), 99 (16.8 %), 60 (10.2 %), 7 (1.2 %), 124 (21.1 %), and 139 (23.6 %) of 588 OLP patients have microcytosis, blood Hb, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively.[1] Our findings suggest that not all OLP patients with serum iron deficiency have microcytosis. Other concomitantly-present factors such as serum vitamin B12 and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity may also influence the size of erythrocytes in the OLP patients. In this study, the 588 OLP patients were divided into two groups: 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients. Complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in these 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 age- and sex-matched healthy control subjects were measured and compared. The major purpose of this study was to assess whether there were significantly higher frequencies of blood Hb, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in these 78 microcytosis/OLP patients or 510 non-microcytosis/OLP patients than in 588 healthy control subjects. In addition, we also evaluated whether 78 microcytosis/OLP patients might have significantly higher frequencies of anemia and serum iron deficiency than 510 non-microcytosis/OLP patients.

Materials and methods

Subjects

This study consisted of 588 OLP patients including 78 microcytosis/OLP patients (10 men and 68 women, age range 24—84 years, mean age 51.2 ± 13.0 years) and 510 non-microcytosis/OLP patients (100 men and 410 women, age range 20—88 years, mean age 56.5 ± 14.2 years). For each OLP patients, one age- (±2 years of each patient's age) and sex-matched healthy control subject was selected. Thus, 588 healthy control subjects (110 men and 478 women, age range 20—89 years, mean age of 56.0 ± 14.1 years) were selected and included in this study. These 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 healthy control subjects were retrieved from our previous study.[1] All OLP patients and healthy control subjects were consecutively seen, diagnosed, and treated at the Department of Dentistry, National Taiwan University Hospital (NTUH) from July 2007 to June 2023. The clinical and histopathological criteria for the selection of 588 OLP patients were described previously.[1,7–13] However, OLP patients with a history of betel quid chewing, heavy alcohol use, autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, pemphigus vulgaris, etc.), inflammatory diseases, malignancy, recent surgery, or systemic conditions like liver, kidney, coronary artery, or stroke diseases were excluded from this study.[1,7–13] The healthy control subjects were individuals without any oral mucosal or systemic illnesses and with no more than dental caries or mild

periodontal disease. None of the OLP patients had received medication for OLP for at least three months before participating in the study.

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

After obtaining the informed consent forms, the blood samples were drawn from 588 OLP patients and 588 healthy control subjects for determination of complete blood count and serum iron, vitamin B12, folic acid, and homocysteine concentrations by the routine tests performed in the Department of Laboratory Medicine, NTUH.[1,7–38]

Determination of serum gastric parietal cell antibody level

The serum samples prepared from the blood samples of all 588 OLP patients and 588 healthy control subjects were used for determination of the GPCA level by the indirect immunofluorescence technique with rat stomach as a substrate as described previously.[1,7–38] Sera were scored as positive when they produced fluorescence at a dilution of 10-fold or more.

Statistical analysis

The mean corpuscular volume (MCV) and mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels were compared between any two of three groups of subjects including 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 healthy control subjects by Student's *t*-test. The differences in frequencies of microcytosis (defined as MCV $<$80 fL),[1–4] macrocytosis (defined as MCV $\geq$100 fL),[34–38] blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity were compared between any two of three groups of subjects including 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 healthy control subjects by chi-square test. The result was considered to be significant if the *P*-value was less than 0.05.

Results

Comparisons of MCV and mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels between any two of the three groups of subjects including 78 microcytosis/OLP patients, 510 non-microcytosis/OLP patients, and 588 healthy control subjects are shown in Table 1. Because men usually had higher mean blood Hb and iron levels than women, these two mean levels were calculated separately for men and women. We found that 78 microcytosis/OLP patients had significantly lower MCV, mean blood Hb (for men and women), iron (for women only), vitamin B12, and folic acid levels and significantly higher serum homocysteine level than 588 healthy control subjects (all *P*-values $<$0.005, Table 1). Moreover, 78 microcytosis/OLP patients had a significantly lower MCV

Table 1 Comparisons of mean corpuscular volume (MCV), mean blood concentrations of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine between any two of three groups of subjects including 78 oral lichen planus (OLP) patients with microcytosis (microcytosis/OLP patients, MCV $<$80 fL), 510 OLP patients without microcytosis (non-microcytosis/OLP patients), and 588 healthy control subjects.

Group	MCV (fL)	Hb (g/dL)		Iron (μg/dL)		Vitamin B12 (pg/mL)	Folic acid (ng/mL)	Homocysteine (μM)
		Men	Women	Men	Women			
Microcytosis/OLP patients (n = 78)	70.6 ± 5.7	12.9 ± 1.9 (n = 10)	11.2 ± 1.4 (n = 68)	93.0 ± 55.6 (n = 10)	61.1 ± 34.4 (n = 68)	576.3 ± 257.0	12.1 ± 5.8	9.0 ± 3.3
[a]*P*-value	<0.001	<0.001	<0.001	0.301	<0.001	<0.001	<0.001	0.002
[b]*P*-value	<0.001	<0.001	<0.001	0.586	<0.001	0.901	0.356	0.368
Non-microcytosis/OLP patients (n = 510)	91.1 ± 4.8	14.7 ± 1.4 (n = 100)	13.0 ± 1.1 (n = 410)	99.7 ± 34.8 (n = 100)	86.4 ± 28.0 (n = 410)	572.4 ± 259.3	12.8 ± 6.3	9.4 ± 3.7
[a]*P*-value	0.007	0.002	<0.001	0.369	<0.001	<0.001	<0.001	<0.001
Healthy control subjects (n = 588)	90.4 ± 3.8	15.2 ± 0.8 (n = 110)	13.5 ± 0.8 (n = 478)	103.6 ± 27.9 (n = 110)	96.7 ± 27.4 (n = 478)	682.6 ± 231.7	14.7 ± 5.8	8.2 ± 1.9

[a] Comparisons of means of parameters between 78 microcytosis/OLP patients or 510 non-microcytosis/OLP patients and 588 healthy control subjects by Student's *t*-test.
[b] Comparisons of means of parameters between 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients by Student's *t*-test.

and lower mean blood Hb (for men and women) and serum iron levels (for women only) than 510 non-microcytosis/OLP patients (all *P*-values <0.001, Table 1). Furthermore, 510 non-microcytosis/OLP patients had significantly lower mean blood Hb (for men and women), serum iron (for women only), vitamin B12, folic acid levels as well as significantly higher MCV and mean serum homocysteine level than 588 healthy control subjects (all *P*-values <0.01, Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV <80 fL,[1–4] and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.[39] Furthermore, patients with the serum iron level <60 μg/dL,[40] the serum vitamin B12 level <200 pg/mL,[41] or the folic acid level <4 ng/mL[42] were defined as having 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) were defined as having hyperhomocysteinemis. By the above-mentioned definitions, 71.8 %, 46.2 %, 10.3 %, 0.0 %, 18.0 %, and 20.5 % of 78 microcytosis/OLP patients and 18.0 %, 12.4 %, 10.2 %, 1.4 %, 21.6 %, and 24.1 % of 510 non-microcytosis/OLP patients had blood Hb, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, both 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients had significantly higher frequencies of blood Hb, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects (all *P*-values <0.001, Table 2). Moreover, 78 microcytosis/OLP patients had significantly higher frequencies of blood Hb and iron deficiencies than 510 non-microcytosis/OLP patients (both *P*-values <0.001, Table 2).

Fifty-six microcytosis/OLP patients and 92 non-microcytosis/OLP patients had anemia (defined as having an Hb concentration <13 g/dL for men and <12 g/dL for women).[1,39] These 148 OLP patients with different types of anemia have been reported previously.[1] In brief, the 56 anemic microcytosis/OLP patients, included 32 with IDA, 19 with thalassemia trait-induced anemia, and 5 with microcytic anemia other than IDA and thalassemia trait-induced anemia.[1] Moreover, the 92 anemic non-microcytosis/OLP patients included 17 with pernicious anemia (PA), 7 with macrocytic anemia other than PA, and 68 with normocytic anemia (Table 3).[1]

Discussion

This study found that both 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients had significantly higher frequencies of anemia, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects. Moreover, approximately 71.8 % and 46.2 % of 78 microcytosis/OLP patients and approximately 18.0 % and 12.4 % of 510 non-microcytosis/OLP patients had anemia and serum iron deficiency, respectively. Therefore, microcytosis/OLP patients had significantly higher frequencies of anemia and serum iron deficiency than non-microcytosis/OLP patients.

Our previous studies demonstrated that atrophic glossitis (AG), burning mouth syndrome (BMS), and OLP patient with anemia, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia tend to have atrophic oral epithelium that is easy penetrated by the physical and

Table 2 Comparisons of frequencies of blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity between any two of three groups of subjects including 78 oral lichen planus (OLP) patients with microcytosis (microcytosis/OLP patients, MCV <80 fL), 510 OLP patients without microcytosis (non-microcytosis/OLP patients), and 588 healthy control subjects.

Group	Patient number (%)					
	Hemoglobin deficiency (Men <13 g/dL, women <12 g/dL)	Iron deficiency (<60 μg/dL)	Vitamin B12 deficiency (<200 pg/mL)	Folic acid deficiency (<4 ng/mL)	Hyperhomo cysteinemia (>12.0 μM)	GPCA positivity
Microcytosis/OLP patients (n = 78)	56 (71.8)	36 (46.2)	8 (10.3)	0 (0)	14 (18.0)	16 (20.5)
[a]*P*-value	<0.001	<0.001	<0.001	NA	<0.001	<0.001
[b]*P*-value	<0.001	<0.001	0.854	0.631	0.561	0.579
Non-microcytosis/OLP patients (n = 510)	92 (18.0)	63 (12.4)	52 (10.2)	7 (1.4)	110 (21.6)	123 (24.1)
[a]*P*-value	<0.001	<0.001	<0.001	0.014	<0.001	<0.001
Healthy control subjects (n = 588)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.7)	10 (1.7)

[a] Comparisons of frequencies of parameters between 78 microcytosis/OLP patients or 510 non-microcytosis/OLP patients and 588 healthy control subjects by chi-square test.
[b] Comparisons of frequencies of parameters between 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients by chi-square test.

Table 3 Anemia types, hematinic deficiencies, and gastric parietal cell antibody (GPCA) positivity in 56 anemic oral lichen planus (OLP) patients with microcytosis (microcytosis/OLP patients) and in 92 anemic OLP patients without microcytosis (non-microcytosis/OLP patients).

Anemia type	Patient number (%)					
	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
Microcytosis/OLP patients (n = 78)						
Iron deficiency anemia	32 (57.1)	<80	32 (100.0)	6 (18.8)	0 (0.0)	9 (28.1)
Thalassemia trait-induced anemia	19 (33.9)	<74	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Other microcytic anemia	5 (8.9)	<80	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Total	56 (100.0)		32 (57.1)	7 (12.5)	0 (0.0)	10 (17.9)
Non-microcytosis/OLP patients (n = 510)						
Pernicious anemia	17 (18.5)	≥100	2 (11.8)	17 (100.0)	0 (0.0)	17 (100.0)
Other macrocytic anemia	7 (7.6)	≥100	0 (0.0)	5 (71.4)	0 (0.0)	2 (28.6)
Normocytic anemia	68 (73.9)	80–99.9	30 (44.1)	12 (17.7)	2 (2.9)	12 (17.7)
Total	92 (100.0)		32 (34.8)	34 (37.0)	2 (2.2)	31 (33.7)

chemical stimulants, finally leading to the occurrence of burning sensation and numbness of oral mucosa in AG, BMS, and OLP patients.[1,14,24] Moreover, the oral mucosa-associated symptoms such as dry mouth, burning sensation, numbness, and dysfunction of taste may interfere with the eating and swallowing function of some of the OLP patients, finally resulting in reduced food intake, anemia, hematinic deficiencies, and hyperhomocysteinemia in a certain percentage of our OLP patients.[1] The iron deficiency and reduced protein intake may cause microcytosis in OLP patients.

Our previous studies demonstrated that of 79 microcytosis/AG patients, 55 (69.6 %) have anemia (including 30 with IDA and 21 with thalassemia trait-induced anemia) and 34 (43.0 %) have iron deficiency.[2,24] Moreover, of 68 microcytosis/BMS patients, 50 (73.5 %) have anemia (including 21 with IDA and 27 with thalassemia trait-induced anemia) and 30 (44.1 %) have iron deficiency.[3,14] In this study, of 78 microcytosis/OLP patients, 56 (71.8 %) had anemia (including 32 with IDA and 19 with thalassemia trait-induced anemia) and 36 (46.2 %) have iron deficiency.[1] These findings indicate that only 69.6 %, 73.5 %, and 71.8 % of 79 AG, 68 BMS, and 78 OLP patients with microcytosis have anemia.[1–3] Furthermore, in 55 (69.6 %) of 79 microcytosis/AG patients, 57 (83.8 %) of 68 microcytosis/BMS patients, and 55 (70.5 %) of 78 microcytosis/OLP patients, the microcytosis could be attributed to iron deficiency or defective synthesis of either α-globin or β-globin in the erythrocytes.[1–3,14,24] The etiologies of microcytosis in the remaining 23 microcytosis/OLP patients may need further studies. We suggest that defects in the synthesis of the heme or protoporphyrine IX may be the possible causes resulting in microcytosis in some of these 23 microcytosis/OLP patients.

The group of 510 non-microcytosis/OLP patients included 474 normocytosis/OLP patients (defined as having MCV between 80 and 99.9 fL) and 36 macrocytosis/OLP patients (defined as having MCV ≥100 fL).[1] The normocytic anemia is discovered in 68 (14.4 %) of 474 normocytosis/OLP patients.[1] Moreover, our previous studies also found normocytic anemia in 117 (12.4 %) of 944 normocytosis/AG patients and in 95 (12.3 %) of 770 normocytosis/BMS patients. These findings suggest that only 12.3–14.4 % of AG, BMS, and OLP patients with normocytosis have normocytic anemia. Although the normocytic anemia was predominantly associated with chronic diseases, inflammatory diseases, infections, bone marrow hypoplasia, decreased production of erythropoietin or a poor response to erythropoietin, hemolytic disorders, mild but persistent blood loss from gastrointestinal tract, and cytokine-induced suppression of erythropoiesis,[43–46] deficiencies of iron, vitamin B12, and folic acid were observed in 44.1 %, 17.7 %, and 2.9 % of 68 OLP patients with normocytic anemia.[1] Iron deficiency causes microcytic erythrocytes[5,39] and deficiencies of vitamin B12 and folic acid lead to macrocytic erythrocytes.[34–38,41,42,47] If the anemic patients have concomitant deficiencies of iron, vitamin B12, and folic acid, they may have normocytic anemia with erythrocytes of mean normal size.[47]

Our previous studies revealed PA in 22 (53.7 %) of 41 macrocytosis/AG patients and in 15 (32.6 %) of 46 macrocytosis/BMS patients. In this study, PA is identified in 17 (47.2 %) of 36 macrocytosis/OLP patients.[1] These results indicate nearly 50 % of the AG or OLP patients with macrocytosis may have PA, but approximately one-third of the BMS patients with macrocytosis may have PA. In this study, all the 17 PA patients have vitamin B12 deficiency and serum GPCA positivity.[1,36,37] Moreover, 2 (11.8 %) of 17 OLP patients with PA also have serum iron deficiency. Patients with GPCA positivity have a reduced production of intrinsic factor and hydrochloric acid which in turn result in a decreased absorption of vitamin B12 from terminal ileum and a reduced absorption of iron from the stomach and the first part of duodenum, respectively.[5,48–50] The above-mentioned statement can explain why 11.8 % of 17 OLP patient with PA may also have iron deficiency.[48]

Homocysteine is formed during methionine metabolism.[51] Both vitamin B12 and folic acid function as coenzymes for the conversion of homocysteine to methionine.[52] Thus, patients with vitamin B12 and/or folic acid deficiencies may have hyperhomocysteinemia.[1,9,16,17,51–53] Our previous studies 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 BMS or AG.[15,25] In this study, hyperhomocysteinemia, vitamin B12 deficiency, and folic acid deficiency were observed in 18.0 %, 10.3 %, and 0.0 % of 78 microcytosis/OLP patients and in 21.6 %, 10.2 %, and 1.4 % of 510 non-microcytosis/OLP patients respectively. These data suggest that hyperhomocysteinemia in our 78 microcytosis/OLP patients or 510 non-microcytosis/OLP patients are only minorly due to deficiencies of vitamin B12 and/or folic acid. Other factors such as a dysfunction of enzymes and cofactors associated with the process of homocysteine biosynthesis, excessive methionine intake, certain diseases (chronic renal failure, hypothyroidism, PA or sickle cell anemia, and malignant tumors in the breast, ovary, and pancreas), and side effects of some drugs (cholestyramine, metformin, methotrexate, nicotinic acid, fibric acid derivatives, and oral contraceptive pills) may also be considered as the causes resulting in hyperhomocysteinemia in our microcytosis/OLP patients or non-microcytosis/OLP patients.[54] Further studies are needed to explore the real etiologies for causing hyperhomocysteinemia in our 588 OLP patients.

The results of this study indicate that there are significantly higher frequencies of anemia, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity in our 78 microcytosis/OLP patients and 510 non-microcytosis/OLP patients than in 588 healthy control subjects. Moreover, 78 microcytosis/OLP patients have significantly higher frequencies of blood Hb and iron deficiencies than 510 non-microcytosis/OLP patients.

Declaration of competing interest

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

Acknowledgments

None.

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