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Original Article

Anemia, hematinic deficiencies, and hyperhomocysteinemia in younger and older oral lichen planus patients

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Abstract *Background/purpose:* Our previous study found that 25.2 %, 16.8 %, 10.2 %, 1.2 %, and 21.1 % of 588 oral lichen planus (OLP) patients have anemia, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. This study mainly assessed the anemia, hematinic deficiencies, and hyperhomocysteinemia in 190 younger (≤50 years old) and 398 older (>50 years old) OLP patients.
Materials and methods: The blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels in 190 younger and 398 older OLP patients were measured and compared with the corresponding levels in 190 younger (≤50 years old) and 398 older (>50 years old) healthy control subjects (HCSs), respectively.
Results: We discovered that 190 younger OLP patients had significantly lower mean blood Hb and serum iron, vitamin B12, and folic acid levels than 190 younger HCSs. Moreover, 398 older

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OLP patients had significantly lower mean blood Hb, and serum iron, vitamin B12, and folic acid levels and significantly higher mean serum homocysteine level than 398 older HCSs. In addition, 190 younger OLP patients had significantly lower mean serum vitamin B12, folic acid, and homocysteine levels, and a significantly higher frequency of iron deficiency and significantly lower frequencies of vitamin B12 deficiency and hyperhomocysteinemia than 398 older OLP patients.

Conclusion: The younger OLP patients do have significantly lower mean serum vitamin B12 and folic acid levels, and a significantly higher frequency of serum iron deficiency but a significantly lower frequency of serum vitamin B12 deficiency than the older OLP patients.

Introduction

Oral lichen planus (OLP) is a T lymphocyte-mediated chronic inflammatory oral mucosal disease that is more commonly observed in middle-aged and elderly female patients.[1,2] OLP lesions frequently occur on the buccal mucosa, tongue, and gingiva and always show a bilateral and symmetric distribution on the oral mucosa.[1] Clinically, OLP can present mainly in six forms, including reticular, papular, plaque-like, erosive/atrophic, ulcerative, and bullous types.[1] Patients with erosive/atrophic or ulcerative OLP may experience oral symptoms, such as pain and burning sensation in the oral mucosa when consuming irritating foods or drinks. These uncomfortable oral symptoms can lead to reduced food intake and in turn result in anemia, hematinic deficiencies, and hyperhomocysteinemia in a certain percentage of OLP patients.[2]

Our previous studies investigated whether there are significant disparities in anemia, hematinic deficiencies, and hyperhomocysteinemia between younger and old atrophic glossitis (AG) or burning mouth syndrome (BMS) patients.[3,4] We found that the younger AG patients do have significantly lower mean serum vitamin B12 and folic acid levels, a significantly higher frequency of serum iron deficiency, and a significantly lower frequency of hyperhomocysteinemia than the older AG patients.[3] In addition, the younger BMS patients do have higher mean blood Hb level, significantly lower mean serum vitamin B12 and folic acid levels, and significantly higher frequencies of serum iron and folic acid deficiencies than the older BMS patients.[4]

To the best of our knowledge, none of previous studies compared the complete blood count data, serum iron, vitamin B12, folic acid, homocysteine, and gastric parietal cell antibody (GPCA) levels between a large group of younger ($\leq$50 years old) and older (>50 years old) OLP patients. Therefore, in this study, we divided the 588 OLP patients into 190 younger and 398 older OLP patients. We mainly evaluated whether the 190 younger OLP patients had significantly lower mean blood hemoglobin (Hb) and serum iron, vitamin B12, and folic acid levels, significantly higher frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than the 398 older OLP patients. We also assessed whether there were significantly higher frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in the 190 younger or the 398 older OLP patients than in the 190 younger ($\leq$50 years old) or the 398 older (>50 years old) healthy control subjects (HCSs), respectively.

Materials and methods

Participants

This study included 190 younger OLP patients (54 men and 136 women; age range 20—50 years, mean age 39.8 $\pm$ 7.9 years) and 398 older OLP patients (56 men and 342 women; age range 51—88 years, mean age 63.5 $\pm$ 9.1 years).[2] For one OLP patient, one age- ($\pm$2 years of each patient's age) and sex-matched HCS was selected. Thus, 190 age- and sex-matched younger HCSs (54 men and 136 women; age range 20—50 years, mean age 40.0 $\pm$ 7.9 years) and 398 age- and sex-matched older HCSs (56 men and 342 women; age range 51—89 years, mean age 63.6 $\pm$ 9.2 years) were selected and included in this study.[2] All the OLP patients and HCSs were seen consecutively, diagnosed, and treated in the Department of Dentistry of National Taiwan University Hospital (NTUH) from July 2007 to June 2023. The 588 OLP patients were selected according to the following criteria: (i) a typical clinical presentation of radiating grayish-white Wickham striae, papules and plaques, separately or in combination, and erosion or ulceration on the oral mucosa; (ii) the OLP lesions had a bilateral and symmetric distribution on the oral mucosa. In 25 OLP patients the clinical diagnosis of OLP was uncertain, thus, an incisional biopsy of the typical oral mucosal lesion was performed. When the biopsy specimens showed the characteristic features of OLP, that is, hyperkeratosis or parakeratosis, a slightly acanthotic epithelium with liquefaction degeneration of the basal epithelial cells, a pronounced band-like lymphocytic infiltrate in the lamina propria, and the absence of epithelial dysplasia, the histopathological diagnosis of OLP was confirmed.[1,2,5—10] However, all OLP patients with areca quid chewing habit, 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. In addition, all OLP patients with serum creatinine concentrations indicative of renal dysfunction (ie, >131 μmol/L for men and >115 μmol/L for women), and who reported a history of stroke, heavy alcohol use, or diseases of the liver, kidney, or coronary arteries were also excluded.[2,5–10] HCSs had either dental caries or mild periodontal diseases but did not have any oral mucosal or systemic diseases. None of the OLP patients had taken any prescription medication for OLP at least 3 months before entering the study.

The blood samples were drawn from 588 OLP patients and 588 HCSs 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 HCSs 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.[2–38]

Determination of serum gastric parietal cell antibody level

The serum GPCA level was detected by the indirect immunofluorescence technique with the rat stomach as the substrate as described previously.[2–38] 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 190 younger or 398 older OLP patients and 190 younger or 398 older HCSs, respectively, as well as between 190 younger and 398 older OLP patients were performed by Student's *t*-test. The differences in frequencies of microcytosis (MCV <80 fL),[28–32] macrocytosis (MCV ≥100 fL),[33–38] blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity between 190 younger or 398 older OLP patients and 190 younger or 398 older HCSs, respectively, as well as between 190 younger and 398 older OLP patients were compared by chi-square test. In addition, the differences in frequencies of 6 different types of anemia between 190 younger and 398 older OLP patients were also 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 190 younger and 398 older OLP patients and in 190 younger and 398 older HCSs are shown in Table 1. We found that 190 younger OLP patients had significantly lower MCV, mean blood Hb, and serum iron, vitamin B12, and folic acid levels than 190 younger HCSs (all *P*-values <0.01, Table 1). Although the 190 younger OLP patients also had higher mean serum homocysteine level than the 190 younger HCSs, the difference was not significant ($P = 0.295$) (Table 1). Moreover, 398 older OLP patients had significantly lower MCV, mean blood Hb and serum iron, vitamin B12, and folic acid levels, and significantly higher mean serum homocysteine level than 398 older HCSs (all *P*-values <0.05, Table 1). In addition, 190 younger OLP patients had significantly lower MCV and mean serum vitamin B12, folic acid, and homocysteine levels than 398 older OLP patients (all *P*-values <0.05, Table 1). However, no significant differences in the mean blood Hb and serum iron levels were found between 190 younger and 398 older OLP patients (Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV <80 fL,[28–32] macrocytosis of erythrocyte was defined as having MCV ≥100 fL,[33–38] 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 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 HCSs plus two standard deviations) were defined as having hyperhomocysteinemia.[2] By the above-mentioned definitions, 21.1 %, 3.2 %, 25.8 %, 24.2 %, 5.8 %, 2.6 %, 15.8 %, and 14.2 % of 190 younger OLP patients and 9.5 %, 7.5 %, 24.9 %, 13.3 %, 12.3 %, 0.5 %, 23.6 %, and 28.1 % of 398 older 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 (Table 2). Moreover, 190 younger OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron, and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 190 younger HCSs (all *P*-values <0.05, Table 2). Furthermore, 398 older OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 398 older HCSs (all *P*-values <0.001, Table 2). In addition, 190 younger OLP patients had significantly higher frequencies of microcytosis and serum iron deficiencies as well as significantly lower frequencies serum vitamin B12 deficiency, hyperhomocysteinemia, and GPCA positivity than 398 older OLP patients (all *P*-values <0.05, Table 2).

Forty-nine younger and 99 older OLP patients had anemia (defined as having an Hb concentration <13 g/dL for men and <12 g/dL for women).[39] Of the 49 anemic younger OLP patients, three had pernicious anemia (PA, defined as

Table 1 Comparisons of mean corpuscular volume (MCV) and mean blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels between 190 younger (≤50 years old) or 398 older (>50 years old) oral lichen planus (OLP) patients and 190 younger (≤50 years old) or 398 older (>50 years old) healthy control subjects (HCSs), respectively, as well as between 190 younger and 398 older OLP patients.

Group	MCV (fL)	Hb (g/dL)	Iron (μg/dL)	Vitamin B12 (pg/mL)	Folic acid (ng/mL)	Homocysteine (μM)
Younger OLP patients (n = 190)	85.5 ± 9.0	13.2 ± 1.8	82.5 ± 35.0	538.0 ± 227.4	10.3 ± 5.0	8.6 ± 3.4
[a]*P*-value	<0.001	<0.001	<0.001	0.005	<0.001	0.295
[b]*P*-value	<0.001	0.141	0.084	0.024	<0.001	<0.001
Older OLP patients (n = 398)	89.7 ± 8.0	13.0 ± 1.4	87.4 ± 30.7	589.5 ± 271.2	13.8 ± 6.4	9.7 ± 3.7
[a]*P*-value	0.013	<0.001	<0.001	<0.001	<0.001	<0.001
Younger HCSs (n = 190)	89.4 ± 3.8	14.0 ± 1.1	99.8 ± 32.0	602.4 ± 215.2	12.9 ± 5.4	8.3 ± 2.0
Older HCSs (n = 398)	90.8 ± 3.7	13.8 ± 1.0	97.2 ± 25.2	720.9 ± 229.7	15.5 ± 5.8	8.2 ± 1.8

[a] Comparisons of means of parameters between 190 younger or 398 older OLP patients and 190 younger or 398 older HCSs by Student's *t*-test, respectively.
[b] Comparisons of means of parameters between 190 younger and 398 older OLP patients 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 (Hb) and serum iron, vitamin B12, and folic acid deficiencies, and gastric parietal cell antibody (GPCA) positivity between 190 younger (≤50 years old) or 398 older (>50 years old) oral lichen planus (OLP) patients and 190 younger (≤50 years old) or 398 older (>50 years old) healthy control subjects (HCSs), respectively, as well as between 190 younger and 398 older OLP patients.

Group	Patient number (%)							
	Microcytosis (MCV <80 fL)	Macrocytosis (MCV ≥100 fL)	Hb 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)	Hyperhomocysteinemia (>12.0 μM)	GPCA positivity
Younger OLP patients (n = 190)	40 (21.1)	6 (3.2)	49 (25.8)	46 (24.2)	11 (5.8)	5 (2.6)	30 (15.8)	27 (14.2)
[a]*P*-value	<0.001	0.040	<0.001	<0.001	0.002	0.072	<0.001	<0.001
[b]*P*-value	<0.001	0.059	0.891	<0.001	0.022	0.069	0.039	<0.001
Older OLP patients (n = 398)	38 (9.5)	30 (7.5)	99 (24.9)	53 (13.3)	49 (12.3)	2 (0.5)	94 (23.6)	112 (28.1)
[a]*P*-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.479	<0.001	<0.001
Younger HCSs (n = 190)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.1)	3 (1.6)
Older HCSs (n = 398)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.5)	7 (1.8)

[a] Comparisons of frequencies of parameters between 190 younger or 398 older OLP patients and 190 younger or 398 older HCSs by chi-square test, respectively.
[b] Comparisons of frequencies of parameters between 190 younger and 398 older OLP patients by chi-square test.

having anemia, an MCV ≥100 fL, a serum vitamin B12 level <200 pg/mL, and the presence of serum GPCA positivity),[33–35] one had macrocytic anemia (defined as having anemia and an MCV ≥100 fL) other than PA,[33–35] 15 had normocytic anemia (defined as having anemia and an MCV between 80 fL and 99.9 fL),[43–46] 19 had iron deficiency anemia (IDA, defined as having anemia, an MCV <80 fL, and a serum iron level <60 μg/dL),[28,39] 10 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),[47] and one had microcytic anemia (defined as having anemia and an MCV <80 fL)[28–32] other than IDA and thalassemia trait-induced anemia. Thus, by the strict WHO criteria the IDA (19/49, 38.8 %) and

Table 3 Comparison of frequencies of 6 different types of anemia between 190 younger (≤50 years old) and 398 older (>50 years old) oral lichen planus (OLP) patients.

Anemia type	Patient number (%)		[a]*P*-value
	Younger OLP patients (n = 190)	Older OLP patients (n = 398)	
Pernicious anemia	3 (1.6)	14 (3.5)	0.294
Other macrocytic anemia	1 (0.5)	6 (1.5)	0.536
Normocytic anemia	15 (7.9)	53 (13.3)	0.074
Iron deficiency anemia	19 (10.0)	13 (3.3)	0.002
Thalassemia trait-induced anemia	10 (5.3)	9 (2.3)	0.094
Other microcytic anemia	1 (0.5)	4 (1.0)	0.912
Total	49 (25.8)	99 (24.9)	0.891

[a] Comparison of frequencies of 6 different types of anemia between 190 younger and 398 older OLP patients by chi-square test.

normocytic anemia (30.6 %, 15/49) were the two most common types of anemia in our 49 anemic younger OLP patients (Table 3).

Of the 99 anemic older OLP patients, 14 had PA,[33–35] 6 had macrocytic anemia other than PA,[33–38] 53 had normocytic anemia,[43–46] 13 had IDA,[28,39] 9 had thalassemia trait-induced anemia,[47] and four had microcytic anemia[28–32] other than IDA and thalassemia trait-induced anemia. Therefore, by the strict WHO criteria the normocytic anemia (53.5 %, 53/99) and PA (14.1 %, 14/99) were the two most common types of anemia in our 99 anemic older OLP patients (Table 3). In addition, 190 younger OLP patients had a significantly higher frequency of IDA than 398 older OLP patients ($P = 0.002$, Table 3).

Discussion

This study revealed that the 190 younger OLP patients exhibited significantly lower MCV and lower mean serum levels of vitamin B12, folic acid, and homocysteine compared with the 398 older OLP patients. They also showed a higher prevalence of microcytosis and serum iron deficiency but lower frequencies of serum vitamin B12 deficiency, hyperhomocysteinemia, and serum GPCA positivity. These findings suggest that age-related physiological and hormonal differences may influence hematological indices, hematinic status, and immunological profiles in OLP patients. To better interpret our results, it is necessary to consider the demographic and hormonal characteristics of the two age groups of OLP patients studied.

In our cohort, the 190 younger OLP patients (≤50 years) comprised 54 men (28.4 %) and 136 women (71.6 %) with a mean age of 39.8 years. Most younger men likely had sufficient androgen levels, while most younger women were still menstruating and maintained adequate estrogen levels. By contrast, the 398 older OLP patients (>50 years) consisted of 56 men (14.1 %) and 342 women (85.9 %) with a mean age of 63.5 years. In the older OLP patients, men may have experienced slight declines in total body androgens, and nearly all women were likely postmenopausal, with correspondingly lower estrogen levels. Androgens are well known to stimulate erythropoiesis by promoting erythropoietin release, enhancing bone marrow activity, and facilitating iron incorporation into red blood cells.[48–50] Estrogens, however, do not exert a similar erythropoietic effect and can even suppress red blood cell production under certain conditions, such as chronic mountain sickness.[51] Following menopause, ovarian estrogen production ceases, leading to reduced estrogen levels but increased total body iron due to the cessation of menstrual blood loss. Nevertheless, estrogen deficiency upregulates hepcidin, which inhibits intestinal iron absorption and can paradoxically lower serum iron levels.[52] Iron balance in women is also affected by reproductive history and menstrual losses. Each healthy pregnancy depletes the maternal body of approximately 500 mg of iron, while menstrual blood losses vary widely, resulting in an average daily iron loss of about 2 mg during childbearing years.[53] These chronic iron losses make iron deficiency anemia twice as common in females compared with males, particularly during the reproductive years.[54] Additionally, women typically consume less dietary iron than men, requiring greater absorption efficiency to maintain their iron homeostasis.

Taken together, these biological and demographic factors may explain our observations. In younger OLP patients, adequate androgen levels support erythropoiesis and help maintain blood Hb and red blood cell production, whereas menstruation and past pregnancies increase the risk of iron depletion, leading to higher rates of iron deficiency despite relatively higher blood Hb levels. Conversely, in older OLP patients, menopause eliminates menstrual iron losses and generally improves iron status, but declining androgen levels and age-related physiological changes may blunt erythropoiesis. The net result is that the younger OLP patients present with higher blood Hb, lower serum iron, and more frequent iron deficiency compared with the older OLP patients, reflecting the complex interplay among age, hormones, and iron metabolism in OLP patients.[48–54]

We further explained why the younger OLP patients had the significantly lower mean serum vitamin B12 and folic acid levels, a significantly lower frequency of vitamin B12 deficiency, and a slightly higher frequency of folic acid deficiency than the older OLP patients. Previous studies discovered significantly lower mean folate levels in buccal mucosal cells and sera of 25 smokers than in those of 34 non-smokers.[55] Piyathilake et al.[56] also demonstrated lower buccal mucosal cell folate and vitamin Bl2 concentrations in 39 current smokers than in 60 noncurrent smokers.[56] Our previous study of serum vitamin B12 and folic acid levels in oral precancer patients also found significantly lower mean serum folic acid levels in 87 cigarette smokers than in 44 non-smokers and in 26 smokers consuming >20 cigarettes per day than in 61 smokers consuming ≤20 cigarettes per day.[57] The findings of above-mentioned studies indicate the

existence of vitamin B12 and folic acid deficiencies in the sera and oral mucosal cells of the cigarette smokers. Thus, we suggest that the mechanisms of vitamin B12 and folic acid deficiencies may result from elevated vitamin B12 and folic acid consumption in response to rapid cell proliferation or tissue repair caused by the irritation or damage of oral mucosal cells by the carcinogens in tobacco.[58] In this study, OLP patients with the areca quid chewing habits and heavy alcohol use were excluded. Moreover, we did not assess the frequencies of cigarette smoking in our 190 younger and 398 older OLP patients. Because there is a significantly higher prevalence of cigarette smoking habit in younger people than in older people in Taiwan,[59] we strongly suggest that the cigarette smoking habit may be the major factors that result in the lower mean serum vitamin B12 and folic acid levels and higher frequency of folic acid deficiency in the younger OLP patients than in the older OLP patients.[55–59] Furthermore, the frequency of GPCA positivity was significantly higher in the 398 older OLP patients (28.1 %) than in the 190 younger OLP patients (14.2 %). Because the presence of GPCA can result in malabsorption of vitamin B12 in the terminal ileum, this finding could explain why the frequency of vitamin B12 deficiency was significantly higher in the 398 older OLP patients (12.3 %) than in the 190 younger OLP patients (5.8 %).[60,61] In addition, although the younger people tend to have more active physiological function including relatively higher intestinal absorption rate and better regeneration and tissue repair functions, these younger OLP patients should have more severe deficiencies of vitamin B12 and folic acid to acquire the disease of OLP. Taking the above-mentioned several factors together, it is not surprised to see the significantly lower mean serum vitamin B12 and folic acid levels and a slightly higher frequency of folic acid deficiency but a significantly lower frequency of Vitamin B12 deficiency in the younger OLP patients than in the older OLP patients.

Homocysteine is formed during methionine metabolism.[62] Both vitamin B12 and folic acid function as coenzymes for the conversion of homocysteine to methionine.[63] Thus, patients with vitamin B12 and/or folic acid deficiencies may have hyperhomocysteinemia. A previous study has shown that a supplementation with folic acid and vitamins B12 and B6 can reduce blood homocysteine levels.[64] 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 BMS or AG.[65,66] In this study, of the total of 588 OLP patients, 60 (10.2 %) had vitamin B12 deficiency, but only 7 (1.2 %) had folic acid deficiency, suggesting that the frequency of vitamin B12 deficiency may play a major role in influencing the frequency of hyperhomocysteinemia in OLP patients.[63,64] Therefore, the significantly higher frequencies of the GPCA positivity and vitamin B12 deficiency in 398 older OLP patients than in 190 younger OLP patients can explain why there is a significantly higher frequency of hyperhomocysteinemia in 398 older OLP patients than in 190 younger OLP patients (Table 2).

In this study, the younger OLP patients had a significantly higher frequency of IDA (10.0 %) than the older OLP patients (3.3 %, $P = 0.002$). This could be due to the findings that the 190 younger OLP patients had a lower mean serum iron level (82.5 ± 35.0 μg/dL) than the 398 older OLP patients (87.4 ± 30.7 μg/dL) and a significantly higher frequency of serum iron deficiency (24.2 %) than the 398 older OLP patients (13.3 %, $P < 0.001$).

Regarding the strengths and limitations of this study, one of the primary strengths of this study is its large sample size and the inclusion of well-matched control groups, which enhances the statistical power and generalizability of our findings. The strict inclusion and exclusion criteria also helped to minimize confounding factors such as comorbid autoimmune diseases, malignancies, and renal or hepatic dysfunction. However, several limitations should be acknowledged. First, the cross-sectional design precludes any inference of causality between OLP and the observed hematologic abnormalities. It remains unclear whether these deficiencies contribute to OLP pathogenesis or are consequences of disease-related dietary limitations. Second, although we excluded patients with overt systemic diseases, subclinical conditions affecting nutrient absorption (e.g., celiac disease or *Helicobacter pylori* infection) may still have influence on the results. Third, the detailed clinical OLP subtypes (e.g., erosive vs. reticular) was not included in this study, which could have provided further insights into the correlations between symptom severity and nutrient deficiencies. Lastly, GPCA testing, while indicative of autoimmune gastritis, is not definitive for PA without concurrent evidence of intrinsic factor antibody positivity or gastric biopsy findings.[60,61] Future studies should incorporate these additional parameters for more accurate diagnosis of PA.

This study highlights significant age-related differences in hematologic and immunologic profiles among OLP patients. While both younger and older OLP patients exhibit increased prevalence of anemia and hematinic deficiencies compared to healthy controls, the underlying causes and patterns differ markedly. IDA predominates in younger patients, whereas PA and normocytic anemia are more common in older patients, likely reflecting age-related changes in immunity and nutrient absorption. Moreover, our findings underscore the importance of age-specific screening strategies in OLP patients, which may improve patient outcomes through targeted supplementation and earlier intervention. Furthermore, the younger OLP patients do have significantly lower mean serum vitamin B12 and folic acid levels, and a significantly higher frequency of serum iron deficiency but a significantly lower frequency of serum vitamin B12 deficiency than the older OLP patients. Future prospective and mechanistic studies are needed to explore whether correcting these deficiencies can influence the clinical course of OLP or reduce symptom burden. In addition, longitudinal follow-up would help determine whether these hematinic abnormalities precede or follow the development of OLP, contributing to a more refined understanding of disease pathogenesis.

Declaration of competing interest

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

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