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Original Article

Anemia, hematinic deficiencies, and hyperhomocysteinemia in gastric parietal cell antibody-positive and -negative oral lichen planus patients

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Abstract *Background/purpose:* Our previous study found the serum gastric parietal cell antibody (GPCA) positivity in 23.6 % of oral lichen planus (OLP) patients. This study assessed whether GPCA-positive OLP ($GPCA^{+}OLP$) patients had significantly higher frequencies of macrocytosis, anemia, hematinic deficiencies, and hyperhomocysteinemia than healthy control subjects or GPCA-negative OLP ($GPC\bar{A}OLP$) patients.
Materials and methods: The mean corpuscular volume, blood hemoglobin (Hb), and serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels were measured and compared between any two of three groups of 139 $GPCA^{+}OLP$ patients, 449 $GPCA^{-}OLP$ patients, and 588 healthy control subjects.

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cysteinemia

Results: We found that 139 GPCA $^{+}$ OLP patients had significantly higher frequencies of macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 588 healthy control subjects (all *P*-values <0.001) and significantly higher frequencies of macrocytosis, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 449 GPCA^{-}OLP patients (all *P*-values <0.05). Moreover, 449 GPCA^{-}OLP patients had significantly higher frequencies of macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia than 588 healthy control subjects (all *P*-values <0.01). Pernicious anemia (41.5 %) and normocytic anemia (29.3 %) were the two most common types of anemia in 41 anemic GPCA^{+}OLP patients. Moreover, normocytic anemia (52.3 %), iron deficiency anemia (21.5 %), and thalassemia trait-induced anemia (16.8 %) were the three most common types of anemia in 107 anemic GPCĀOLP patients.

Conclusion: GPCA $^{+}$ OLP patients have significantly higher frequencies of macrocytosis, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than healthy control subjects or GPCĀOLP patients.

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] Our previous study discovered that 139 (23.6 %) of 588 OLP patients have serum gastric parietal cell antibody (GPCA) positivity.[3] Vitamin B12 absorption is a complicated process. In the normal condition of vitamin B12 absorption, food-bound vitamin B12 is released in the stomach and binds to salivary haptocorrin. In the small intestine, food vitamin B12 and biliary vitamin B12 are released from haptocorrin by pancreatic proteases and subsequently bind to intrinsic factor. The intrinsic factor-B12 complex then binds to the cubilin-amnionless receptor on the mucosal cells of the terminal ileum for internalization and release into plasma.[4–7] If the patients have the serum GPCA positivity, GPCA may destroy the gastric parietal cells and cause lack of intrinsic factors and hypochlorhydria. Intrinsic factor deficiency can lead to malabsorption of vitamin B12 and finally resulting in vitamin B12 deficiency, macrocytosis, hyperhomocysteinemia, and pernicious anemia (PA).[4–10] Furthermore, decreased gastric secretion of hydrochloric acid may cause iron malabsorption and subsequent iron deficiency in patients with GPCA positivity.[11,12] Therefore, it is interesting to know whether the serum GPCA-positive OLP (GPCA^{+}OLP) patients have significantly higher frequencies of macrocytosis, anemia, hematinic deficiencies, and hyperhomocysteinemia than healthy control subjects or serum GPCA-negative OLP (GPCĀOLP) patients.

The patients with OLP, burning mouth syndrome (BMS), atrophic glossitis (AG), recurrent aphthous stomatitis, oral submucous fibrosis, and oral precancers are commonly seen in our oral mucosal disease clinic.[3,13–47] The mean frequencies of anemia, serum iron or vitamin B12 deficiency, hyperhomocysteinemia, and GPCA positivity in patients with these 6 kinds of oral mucosal diseases are all found to be between 8 % and 20 %.[3,16,20,30,33,38,39] These findings indicate the importance of checking the blood hemoglobin (Hb) and serum iron, vitamin B12, and homocysteine levels, and serum GPCA positivity in patients with these 6 kinds of oral mucosal diseases before giving them the proper treatments.[3,16,20,30,33,38,39]

Our previous study found that 25.2 %, 16.8 %, 10.2 %, 1.2 %, 21.1 %, and 23.6 % of 588 OLP patients had blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively.[3] Furthermore, 588 OLP patients had significantly higher frequencies of blood Hb and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects.[3] In this study, we further divided the 588 OLP patients into 139 GPCA^{+}OLP patients and 449 GPCA^{-}OLP patients. We tried to assess whether there were significantly higher frequencies of macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia in these 139 GPCA^{+}OLP patients than in 588 healthy control subjects or in 449 GPCA^{-}OLP patients. In addition, we also evaluated whether 449 GPCA^{-}OLP patients still had significantly higher frequencies of macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia than 588 healthy control subjects.

Materials and methods

Subjects

In this study, 139 (20 men and 119 women, age range 29–87 years, mean age 58.8 ± 11.8 years) GPCA^{+}OLP patients and 449 (90 men and 359 women, age range 20–88 years, mean age 54.9 ± 14.7 years) GPCĀOLP patients were collected from the oral mucosal disease clinic of National Taiwan University Hospital (NTUH).[3] For each OLP patient, one age- (within ±2 years) and sex-matched healthy control subject was selected. Thus, 588 age- and sex-matched healthy control subjects (110 men and 478 women, age range 20–89 years, mean age 56.0 ± 14.1 years) were included in this

study.[3] All OLP patients and healthy control subjects were consecutively seen, diagnosed, and treated at the Department of Dentistry, NTUH from July 2007 to June 2023. The 588 OLP patients were selected based on the following criteria: (i) the presence 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 diagnosis of OLP, an incisional biopsy of the typical oral mucosal lesion was performed. The histopathological diagnosis of OLP was confirmed using the criteria described previously.[3,13–19] 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.[3,13–19] The healthy control subjects were individuals without any oral mucosal or systemic illnesses and with no more than dental caries or very mild periodontal disease. None of the OLP patients had received medication for OLP for at least three months before participating in the study.

Blood samples were drawn from 139 GPCA$^+$OLP patients, 449 GPCA$^-$OLP patients, and 588 healthy control subjects to measure complete blood count, serum iron, vitamin B12, folic acid, and homocysteine levels, and serum GPCA positivity. All OLP patients and healthy control subjects provided informed consent before participating in the study. The 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 levels

The complete blood count, as well as serum iron, vitamin B12, folic acid, and homocysteine levels, were measured using routine tests conducted in the Department of Laboratory Medicine at the NTUH.[3,13–47]

Determination of serum gastric parietal cell antibody level

The serum GPCA level was measured using the indirect immunofluorescence technique, with the rat stomach serving as the substrate, as previously described.[3,13–47] Sera were considered positive if they exhibited fluorescence at a dilution of 1:10 or more.

Statistical analysis

The mean corpuscular volume (MCV) and mean blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels were compared between any two of three groups of 139 GPCA$^+$OLP patients, 449 GPCA$^-$OLP patients, and 588 healthy control subjects by Student's *t*-test. The differences in frequencies of microcytosis (defined as MCV $<$80 fL),[40–42] macrocytosis (defined as MCV $\geq$100 fL),[43–47] blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity were compared between any two of three groups of 139 GPCA$^+$OLP patients, 449 GPCA$^-$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 three groups of 139 GPCA$^+$OLP patients, 449 GPCA$^-$OLP patients, and 588 healthy control subjects are shown in Table 1. Because men tended to have higher blood Hb and serum iron levels than women, these two mean

Table 1 Comparisons of mean corpuscular volume (MCV) and mean blood concentrations of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine between any two of three groups of 139 gastric parietal cell antibody (GPCA)-positive oral lichen planus (OLP) patients (GPCA$^+$OLP patients), 449 GPCA-negative OLP patients (GPCA$^-$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			
GPCA$^+$OLP patients (n = 139)	90.5 ± 9.3	14.1 ± 1.5 (n = 20)	12.6 ± 1.3 (n = 119)	91.3 ± 41.0 (n = 20)	79.3 ± 29.6 (n = 119)	454.2 ± 278.3	13.0 ± 5.8	12.2 ± 4.4
[a]*P*-value	0.842	<0.001	<0.001	0.096	<0.001	<0.001	0.002	<0.001
[b]*P*-value	<0.001	0.109	0.109	0.096	0.151	<0.001	0.506	<0.001
GPCA$^-$OLP patients (n = 449)	87.7 ± 8.2	14.7 ± 1.5 (n = 90)	12.8 ± 1.3 (n = 359)	100.8 ± 35.9 (n = 90)	83.9 ± 30.4 (n = 359)	609.6 ± 241.2	12.6 ± 6.3	8.4 ± 2.8
[a]*P*-value	<0.001	0.003	<0.001	0.536	<0.001	<0.001	<0.001	0.172
[c]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 139 GPCA$^+$ OLP or 449 GPCA$^-$OLP patients and 588 healthy control subjects by Student's *t*-test.
[b] Comparisons of means of parameters between 139 GPCA$^+$ OLP and 449 GPCA$^-$OLP patients by Student's *t*-test.
[c] The hematological data of 588 healthy control subjects were retrieved from our previous study.[3]

levels were calculated separately for men and women. We found significantly lower mean blood Hb (for men and women) and serum iron (for women only), vitamin B12, and folic acid levels as well as significantly higher mean serum homocysteine level in GPCA$^+$OLP patients than in healthy control subjects (all *P*-values <0.005, Table 1). Moreover, we also discovered significantly lower mean serum vitamin B12 level and significantly higher MCV and mean serum homocysteine level in GPCA$^+$OLP patients than in GPCA$^-$OLP patients (all *P*-values <0.001, Table 1). Furthermore, GPCA$^-$OLP patients also had significantly lower MCV, mean blood Hb (for men and women) and serum iron (for women only), vitamin B12, and folic acid levels than healthy control subjects (all *P*-values <0.005, Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV <80 fL,[40–42] macrocytosis of erythrocyte was defined as having MCV ≥100 fL,[43–47] and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.[48] Furthermore, patients with the serum iron level <60 μg/dL,[49] the serum vitamin B12 level <200 pg/mL,[50] or the serum folic acid level <4 ng/mL[51] 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) were defined as having hyperhomocysteinemis. By the above-mentioned definitions, 11.5 %, 20.9 %, 29.5 %, 23.7 %, 28.8 %, 0.0 %, and 54.7 % of 139 GPCA$^+$OLP patients and 13.8 %, 1.6 %, 23.8 %, 14.7 %, 4.5 %, 1.6 %, and 10.7 % of 449 GPCA$^-$OLP patients were diagnosed as having microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. We found that 139 GPCA$^+$OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 588 healthy control subjects (all *P*-values <0.001, Table 2) and significantly higher frequencies of macrocytosis, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 449 GPCA$^-$OLP patients (all *P*-values <0.05, Table 2). However, 139 GPCA$^+$OLP patients had significantly lower frequency of serum folic acid deficiency than 449 GPCA$^-$OLP patients ($P = 0.008$, Table 2). Moreover, 449 GPCA$^-$OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia than 588 healthy control subjects (all *P*-values <0.01, Table 2).

We also found that 41 GPCA$^+$OLP and 107 GPCA$^-$OLP patients had anemia (defined as having an Hb concentration <13 g/dL for men and <12 g/dL for women).[48] Of the 41 anemic GPCA$^+$ OLP patients, 17 (41.5 %) had PA (define as having anemia, an MCV ≥100 fL, a serum vitamin B12 level <200 pg/mL, and the presence of serum GPCA positivity),[45–47] 2 (4.9 %) had macrocytic anemia (define as having anemia and an MCV ≥100 fL) other than PA,[43–47] 12 (29.3 %) had normocytic anemia (define as having anemia and an MCV between 80.0 fL and 99.9 fL),[52–55] 9 (21.9 %) had iron deficiency anemia (IDA, defined as having anemia, an MCV <80 fL, and a serum iron level <60 μg/dL),[11,12,48,56] and one (2.4 %) had thalassemia trait-induced anemia (defined as having anemia, a RBC count >5.0 M/μL, an MCV <74 fL, and a Mentzer index (MCV/RBC) < 13) (Table 3).[57] Of the 107 anemic GPCA$^-$OLP patients, 5 (4.7 %) had macrocytic anemia other than PA, 56 (52.3 %) had normocytic anemia, 23 (21.5 %) had IDA, 18 (16.8 %) had thalassemia trait-induced anemia, and 5 (4.7 %) had microcytic anemia other than IDA and thalassemia trait-induced anemia (Table 3).

Discussion

This study investigated the associations among serum GPCA positivity, hematological abnormalities, serum iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia in OLP patients, with a focus on the subgroup of GPCA$^+$OLP patients. Through a comparative analysis involving 139 GPCA$^+$OLP patients, 449 GPCA$^-$OLP patients, and 588 healthy control subjects, we demonstrated that both 139 GPCA$^+$OLP and 449 GPCA$^-$OLP patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 588 healthy control subjects. Moreover, 139 GPCA$^+$OLP patients had significantly higher frequencies of macrocytosis, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 449 GPCA$^-$OLP patients. These two findings suggest that the anemia, hematinic deficiencies, and hyperhomocysteinemia in 139 GPCA$^+$OLP patients and in 449 GPCA$^-$OLP patients can be attributed to the disease of OLP itself. Furthermore, the serum GPCA positivity also plays a significant role in causing the macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia in 139 GPCA$^+$OLP patients.

The serum GPCA can induce destruction of gastric parietal cells, resulting in failure of intrinsic factor production[4–7] and vitamin B12 deficiency that finally leads to macrocytosis, hyperhomocysteinemia, and the status of PA.[4–10] Our previous studies demonstrated that vitamin B12 and folic acid deficiencies can lead to hyperhomocysteinemia in oral mucosal disease patients.[3,16,20,30,33,38,39] Supplementation of multiple B vitamins especially vitamin B12 and folic acid can reduce the serum homocysteine levels in patients with BMS or AG.[21,58] Thus, the higher frequency of macrocytosis, anemia, vitamin B12 deficiency, and hyperhomocysteinemia in GPCA$^+$OLP patients than in GPCA$^-$OLP patients are predominantly due to the serum GPCA positivity in GPCA$^+$OLP patient.[4–10]

This study found significantly higher frequencies of blood Hb and serum iron and vitamin B12, deficiencies, and hyperhomocysteinemia in both 139 GPCA$^+$OLP and 449 GPCA$^-$OLP patients than in 588 healthy control subjects. First, we explained why patients with blood Hb and serum iron, and vitamin B12 deficiencies and hyperhomocysteinemia were likely to develop OLP or OLP with oral mucosal erosion (or erosive OLP). Basically, OLP is a T-cell mediated localized autoimmune oral mucosal disease. Cytotoxic T cells may attack and destroy the basal oral epithelial cells, resulting in erosion of oral epithelium. Moreover, OLP patients with blood Hb deficiency have reduced capacity of the blood to carry oxygen to the oral

Table 2 Comparisons of frequencies of microcytosis (mean corpuscular volume or MCV <80 fL), macrocytosis (MCV ≥100 fL), blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity between any two of three groups of 139 gastric parietal cell antibody (GPCA)-positive oral lichen planus (OLP) patients ($GPCA^{+}$OLP patients), 449 GPCA-negative OLP patients ($GPCA^{-}$OLP patients), and 588 healthy control subjects.

Group	Patient number (%)						
	Microcytosis (MCV <80 fL)	Macrocytosis (MCV ≧ 100 fL)	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)	Hyperhomocysteinemia (>12.0 μM)
$GPCA^{+}$OLP patients (n = 139)	16 (11.5)	29 (20.9)	41 (29.5)	33 (23.7)	40 (28.8)	0 (0.0)	76 (54.7)
[a]*P*-value	<0.001	<0.001	<0.001	<0.001	<0.001	ND	<0.001
[b]*P*-value	0.579	<0.001	0.218	0.018	<0.001	0.008	<0.001
$GPCA^{-}$OLP patients (n = 449)	62 (13.8)	7 (1.6)	107 (23.8)	66 (14.7)	20 (4.5)	7 (1.6)	48 (10.7)
[a]*P*-value	<0.001	0.008	<0.001	<0.001	<0.001	0.008	<0.001
[c]Healthy control subjects (n = 588)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.7)

ND = not done.

[a] Comparisons of frequencies of parameters between 139 $GPCA^{+}$ OLP or 449 $GPCA^{-}$OLP patients and 588 healthy control subjects by chi-square test.

[b] Comparisons of frequencies of parameters between 139 $GPCA^{+}$ OLP and 449 $GPCA^{-}$OLP patients by chi-square test.

[c] The hematological data of 588 healthy control subjects were retrieved from our previous study.[3]

Table 3 Anemia types of 41 anemic gastric parietal cell antibody (GPCA)-positive oral lichen planus (OLP) patients ($GPCA^+OLP$ patients) and of 107 anemic GPCA-negative OLP patients ($GPCA^-OLP$ 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)	Hyper-homocysteinemia (>12.0 μM)
$GPCA^+OLP$ patients (n = 139)						
Pernicious anemia (PA)	17 (41.5)	≥100	2 (11.8)	17 (100.0)	0 (0.0)	17 (100.0)
Macrocytic anemia other than PA	2 (4.9)	≥100	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Normocytic anemia	12 (29.3)	80–99.9	7 (58.3)	3 (25.0)	0 (0.0)	7 (58.3)
Iron deficiency anemia	9 (21.9)	<80	9 (100.0)	5 (55.6)	0 (0.0)	7 (77.8)
Thalassemia trait-induced anemia	1 (2.4)	<74	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Total	41 (100.0)		18 (43.9)	25 (61.0)	0 (0.0)	34 (82.9)
$GPCA^-OLP$ patients (n = 449)						
Macrocytic anemia other than PA	5 (4.7)	≥100	0 (0.0)	5 (100.0)	0 (0.0)	5 (100.0)
Normocytic anemia	56 (52.3)	80–99.9	23 (41.1)	9 (16.1)	2 (3.6)	15 (26.8)
Iron deficiency anemia	23 (21.5)	<80	23 (100.0)	1 (4.3)	0 (0.0)	3 (13.0)
Thalassemia trait-induced anemia	18 (16.8)	<74	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other microcytic anemia	5 (4.7)	<80	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)
Total	107 (100.0)		46 (43.0)	16 (15.0)	2 (1.9)	24 (22.4)

mucosa, finally resulting in atrophy or erosion of the oral mucosa.[2,3] Iron is essential to the normal functioning of oral epithelial cells and the immune functioning of T lymphocytes[56] and the vitamin B12 play important roles in DNA synthesis and cell division of oral epithelial cells and T lymphocytes.[46,59] Moreover, high blood homocysteine level may result in an elevated frequency of thrombosis in the feeding arterioles that supply the oral mucosal cells including oral epithelial cells and subepithelial helper and cytotoxic T lymphocytes.[8,9] Therefore, blood Hb and serum iron and vitamin B12 deficiencies and hyperhomocysteinemia may be easy to cause atrophy or localized immune derangement of the oral mucosa in OLP patients, finally leading to the development of OLP or erosive OLP.

Second, we further explained why OLP patients, especially erosive OLP patients, were prone to have anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia. Our previous study found that erosive OLP patients are very sensitive to hot and spicy food and frequently have burning sensation of the oral mucosa.[1] Moreover, 69.4 % (408) of our 588 OLP patients and 67.6 % (94) of our 139 $GPCA^+OLP$ patients were equal to or greater than 50 years old. Thus, some of these older OLP or $GPCA^+$ OLP patients may be prone to have dry mouth and dysfunction of taste.[1,3] Dry mouth can cause eating and swallowing difficulties. Burning sensation and dysfunction of taste also reduce the willingness to eat food in OLP patients. Thus, we suggest that the dry mouth, burning sensation of the oral mucosa, and dysfunction of taste all may interfere with the eating and swallowing function of OLP patients.[3] The eating and swallowing difficulties may finally lead to reduced food intake that in turn results in anemia, vitamin B12 deficiency, and hyperhomocysteinemia in 25.2 %, 10.2 %, and 21.1 % of our 588 OLP patients as well as in 29.5 %, 28.8 %, and 54.7 % of our 139 $GPCA^+OLP$ patients, respectively.[3]

In this study, 43.9 % and 61.0 % of 41 anemic $GPCA^+OLP$ patients as well as 43.0 % and 15.0 % of 107 anemic $GPC\bar{A}OLP$ patients had iron deficiency and vitamin B12 deficiency, respectively. These findings indicate that the iron and vitamin B12 deficiencies are the two important factors causing anemia in both $GPCA^+OLP$ and $GPC\bar{A}OLP$ patients. The PA (41.5 %), normocytic anemia (29.3 %), and thalassemia trait-induced anemia (21.9 %) were the three most common types of anemia in our 41 anemic $GPCA^+OLP$ patients. Moreover, the normocytic anemia (52.3 %), IDA (21.5 %), and thalassemia trait-induced anemia (16.8 %) were the three most common types of anemia in our 107 anemic $GPC\bar{A}OLP$ patients. The most notable distinction was the increased frequency of PA in 139 $GPCA^+OLP$ patients. Of the 41 anemic $GPCA^+OLP$ patients, 17 (41.5 %) met the diagnostic criteria for PA, while none of the $GPC\bar{A}OLP$ patients did. This strongly supports the role of GPCA in mediating intrinsic factor (IF) deficiency, vitamin B12 malabsorption, and the subsequent vitamin B12 deficiency, finally leading to theHave we correctly interpreted the following funding source(s) and country names you cited in your article: PA, United States? PA in $GPCA^+$ OLP patients rather than in $GPC\bar{A}OLP$ patients.[4–7,45–47] The normocytic anemia was predominantly caused by 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.[52–55] Nevertheless, normocytic anemia in $GPCA^+OLP$ and $GPC\bar{A}OLP$ patients may also be attributed to the iron deficiency with occasional and concomitant vitamin B12 and/or folic acid deficiencies.

The IDA is majorly resulted from the iron deficiency.[11,12,48,56] The etiologies of iron deficiency may include a reduced intake of iron during old-age stage, a

decreased absorption of iron in patients who have celiac disease, gastrectomy, atrophic gastritis, or *Helicobacter pylori* infection or who take antacids, H2-receptor antagonists, or proton pump inhibitors, and chronic blood loss related to excessive menstrual flow, hematuria, epistaxis, hemoptysis, hemodialysis, or gastrointestinal diseases.[11,12,48,56] Moreover, some OLP patients with serum GPCA positivity could not secrete enough hydrochloric acid to help absorb iron from gastric and duodenal mucosae, and this in turn may lead to iron deficiency.[11,12,48,56] The thalassemia trait-induced anemia was predominantly due to gene mutation resulting in insufficient production of either the α-globin or β-globin chains of the Hb molecule.[57]

The results of this study have several important clinical implications. First, GPCA screening in OLP patients may help identify those at risk for PA and related systemic complications. Second, regular monitoring of hematologic indices and serum levels of iron, vitamin B12, folic acid, and homocysteine may be warranted in OLP patients, especially those with GPCA positivity or unexplained anemia. Third, given the high prevalence (54.7 %) of hyperhomocysteinemia in the 139 $GPCA^{+}$OLP patients, early detection and correction of vitamin B12 deficiency may reduce the risk of associated vascular and neuropsychiatric complications. Fourth, addressing iron and B12 deficiencies may also improve general fatigue, mucosal healing, and quality of life in OLP patients.[1,3]

Despite its strengths, this study has several limitations. First, although it included a relatively-large sample size and age- and sex-matched healthy control subjects, it remains a cross-sectional and observational study. Therefore, causality cannot be firmly established. Longitudinal studies are needed to clarify the temporal relationships among GPCA seroconversion, OLP progression, and the development of hematinic deficiencies or PA in OLP patients. Second, dietary intake, gastrointestinal symptoms, and *Helicobacter pylori* infection status were not assessed, although they all may influence iron and vitamin B12 absorption. Incorporating gastroscopy and gastric biopsy data could help further elucidate the degree of atrophic gastritis and its association with GPCA. Third, although our GPCA measurement used a reliable immunofluorescence assay, confirmation with other autoimmune markers (e.g., anti-intrinsic factor antibodies or anti-*Helicobacter pylori* antibodies) could have further strengthened the autoimmune gastritis diagnosis. Finally, we did not assess neurologic or systemic symptoms of vitamin B12 deficiency (e.g., paresthesia, cognitive impairment), which could provide a more complete picture of the clinical relevance of vitamin B12 deficiency.

In conclusion, this study demonstrates that serum GPCA positivity in OLP patients is significantly associated with increased risks of microcytosis, macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia. A considerable portion of $GPCA^{+}$OLP patients fulfill the diagnostic criteria for PA, highlighting the importance of considering systemic autoimmunity and nutritional deficiencies in OLP patients. Even $GPCA^{-}$OLP patients exhibit higher frequencies of hematologic and metabolic abnormalities than healthy control subjects, suggesting that OLP may be part of a broader systemic condition. Clinicians managing OLP should be aware of these potential systemic associations and consider appropriate screening for GPCA positivity, anemia, hematinic deficiencies, and hyperhomocysteinemia in OLP patients. Early diagnosis and treatment may prevent complications and improve OLP patients' clinical outcomes. This study found that 139 $GPCA^{+}$OLP patients had significantly higher frequencies of macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 588 healthy control subjects and significantly higher frequencies of macrocytosis, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 449 $GPCA^{-}$OLP patients. We suggest that the serum GPCA positivity may play a significant role in causing vitamin B12 deficiency that subsequently results in macrocytosis and hyperhomocysteinemia in $GPCA^{+}$OLP patients.

Declaration of competing interest

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

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None.

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