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Original Article

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

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KEYWORDS
Oral lichen planus;
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Abstract *Background/purpose:* Macrocytosis is defined as having the mean corpuscular volume (MCV) $\geq$ 100 fL. This study evaluated whether 36 oral lichen planus (OLP) patients with macrocytosis (macrocytosis/OLP patients) had significantly higher frequencies of anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity than 588 healthy control subjects or 588 OLP patients.
Materials and methods: Complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 36 macrocytosis/OLP patients, 588 OLP patients, and 588 healthy control subjects were measured and compared.

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Gastric parietal cell antibody

Results: We found that 66.7 %, 8.3 %, 91.7 %, 0.0 %, 94.4 %, and 80.6 % of 36 macrocytosis/OLP patients were diagnosed as having blood hemoglobin and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 36 macrocytosis/OLP patients had significantly higher frequencies of blood hemoglobin and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects or 588 OLP patients (all *P*-values <0.001). In addition, 36 macrocytosis/OLP patients also had a significantly higher frequency of serum iron deficiency than 588 healthy control subjects ($P < 0.001$). Pernicious anemia was found in 17 macrocytosis/OLP patients.

Conclusion: There are significantly higher frequencies of anemia and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity in 36 macrocytosis/OLP patients than in 588 healthy control subjects. Moreover, 36 macrocytosis/OLP patients also have significantly higher frequencies of anemia, serum vitamin B12 deficiency, hyperhomocysteinemia, and serum GPCA positivity than 588 OLP patients.

Introduction

According to the World Health Organization (WHO) criteria, erythrocyte macrocytosis is defined as a mean corpuscular volume (MCV) of ≥100 fL.[1–8] The causes of macrocytic anemia include nutritional deficiencies (such as vitamin B12 and/or folic acid deficiency), the use of certain medications (including chemotherapeutic, antiretroviral, and antimicrobial agents), primary bone marrow disorders (e.g., myelodysplasia and leukemia), and various chronic illnesses (such as alcoholism and hypothyroidism).[1–8] Among these, vitamin B12 deficiency is the most common cause of macrocytic anemia. It is important to note that macrocytosis can occur with or without macrocytic anemia.[1–8] Vitamin B12 deficiency may result from several factors, including inadequate dietary intake, impaired release of food-bound vitamin B12, the presence of autoantibodies against gastric parietal cells and/or intrinsic factor, ileal malabsorption, biological competition (such as bacterial overgrowth or tapeworm infection), and defects in transport mechanisms (e.g., transcobalamin II deficiency).[9] Gastric parietal cells produce hydrochloric acid and intrinsic factor, which are essential for iron absorption in the duodenum and proximal jejunum, and vitamin B12 absorption in the terminal ileum, respectively.[9] Severe vitamin B12 deficiency can lead to pernicious anemia (PA). Approximately 85 % of PA patients have gastric parietal cell antibody (GPCA), which lead to destruction of the parietal cells and reduced intrinsic factor production.[10,11] Additionally, 40 %–80 % of PA patients develop intrinsic factor antibodies that block the vitamin B12-binding site of intrinsic factor, thereby impairing vitamin B12 absorption.[12,13]

Patients with oral lichen planus (OLP), atrophic glossitis (AG), burning mouth syndrome (BMS), recurrent aphthous stomatitis, oral submucous fibrosis, or oral precancerous lesions are commonly seen in our oral mucosal disease clinic.[14–47] For individuals diagnosed with any of these six conditions, evaluations often include complete blood count, serum levels of iron, vitamin B12, folic acid, and homocysteine, as well as assessments for gastric parietal cell antibody (GPCA), thyroglobulin antibody, and thyroid microsomal antibody (also known as anti-thyroid peroxidase or anti-TPO antibody).[14–47] These tests help determine whether the patients have anemia, hematinic deficiencies, hyperhomocysteinemia, or are positive for GPCA, thyroglobulin antibody, and thyroid microsomal antibody.[14–47]

Our previous study reported that among 588 OLP patients, the prevalence of blood hemoglobin (Hb) and serum deficiencies in iron, vitamin B12, and folic acid were 25.2 %, 16.8 %, 10.2 %, and 1.2 %, respectively. Additionally, 21.1 % had hyperhomocysteinemia, and 23.6 % tested positive for serum GPCA.[14] In the present study, we analyzed blood data from 36 OLP patients with macrocytosis (referred to as macrocytosis/OLP patients), 588 OLP patients, and 588 healthy control subjects, all drawn from our previous study.[14] For these individuals, we measured complete blood count, serum levels of iron, vitamin B12, folic acid, and homocysteine, as well as serum GPCA levels. The goal was to determine whether the 36 macrocytosis/OLP patients exhibited significantly higher rates of anemia, deficiencies in serum iron, vitamin B12, and folic acid, hyperhomocysteinemia, and GPCA positivity compared to the 588 healthy control subjects or the 588 OLP patients. Furthermore, we evaluated what proportions of the macrocytosis/OLP patients with vitamin B12 deficiency, hyperhomocysteinemia, or GPCA positivity might potentially have PA.

Materials and methods

Subjects

In this study, 36 macrocytosis/OLP patients (5 men and 31 women, mean age 61.8 ± 13.0 years, age range 30–82 years) were selected from 588 OLP patients reported in our previous study.[14] Moreover, the blood examination data of 588 OLP patients (110 men and 478 women, mean age, 55.8 ± 14.1 years, age range 20–88 years) and 588 age- (±2 years of each patient's age) and sex-matched healthy control subjects (110 men and 478 women, mean age, 56.0 ± 14.1 years, age range 20–89 years) were also

retrieved from the same previous study for comparisons.[14] 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.[14] 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.[14–20] 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.[14–47]

Determination of serum gastric parietal cell antibody (GPCA) 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.[14–47] 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 any two of three groups of subjects including 36 macrocytosis/OLP patients, 588 OLP patients, and 588 healthy control subjects were performed by Student's *t*-test. The differences in frequencies of blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity between any two of three groups of subjects including 36 macrocytosis/OLP patients, 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 concentrations in 36 macrocytosis/OLP patients, 588 OLP patients, and 588 healthy control subjects are shown in Table 1. Because men usually had higher blood Hb and serum iron levels than women, these two mean levels were calculated separately for men and women. We found that 36 macrocytosis/OLP patients had significantly lower mean blood Hb (for men and women), serum iron (for women only), and serum vitamin B12 levels as well as a significantly higher MCV and mean serum homocysteine level than 588 healthy control subjects (all *P*-values <0.001 except $P = 0.039$ for women's mean serum iron level, Table 1). Moreover, 36 macrocytosis/OLP patients had significantly lower mean blood Hb (for women only) and serum vitamin B12 levels as well as a significantly higher MCV and mean serum homocysteine level than 588 OLP patients (all *P*-values <0.001, Table 1).

According to the World Health Organization (WHO) criteria, erythrocyte macrocytosis was defined as having an MCV $\geq$100 fL,[1–8] and men with Hb $<$ 13 g/dL and women with Hb $<$ 12 g/dL were defined as having Hb deficiency or anemia.[48,49] Furthermore, patients with the serum iron level $<$60 μg/dL,[50] the serum vitamin B12 level $<$200 pg/mL,[51] or the folic acid level $<$4 ng/mL[52] were defined as having iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the serum homocysteine level $>$12.0 μM (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations) were defined as having hyperhomocysteinemis.[14] By the above-mentioned definitions, 66.7 %, 8.3 %, 91.7 %, 0.0 %, 94.4 %, and 80.6 % of 36 macrocytosis/OLP patients were diagnosed as having blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. In addition, 36 macrocytosis/OLP patients had significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects or 588 OLP patients (all *P*-values <0.001, Table 2). Moreover, 36 macrocytosis/OLP patients also had a significantly higher frequency of serum iron deficiency than 588 healthy control subjects ($P < 0.001$, Table 2).

In this study, OLP patients with PA were defined as having anemia, macrocytosis, vitamin B12 deficiency, and GPCA positivity.[7,8] By this definition, 17 (47.2 %) of 36 macrocytosis/OLP patients had PA. In addition, 17 (70.8 %) of 24 anemic, 17 (51.5 %) of 33 vitamin B12-deficient, 17 (50.0 %) of 34 hyperhomocysteinemic, and 17 (58.6 %) of 29 GPCA-positive macrocytosis/OLP patients had PA. The other 7 anemic macrocytosis/OLP patients had macrocytic anemia other than PA.[14]

Discussion

This study discovered significantly higher frequencies of anemia (66.7 %), serum iron deficiency (8.3 %), serum vitamin B12 deficiency (91.7 %), hyperhomocysteinemia (94.4 %), and serum GPCA positivity (80.6 %) in 36 macrocytosis/OLP patients than in 588 healthy control subjects. These findings suggest that from the nutritional point of view the macrocytosis in OLP patients is attributed majorly to vitamin B12 deficiency, because none of our 36 macrocytosis/OLP patients have folic acid deficiency.[1–6] Of the 24

Table 1 Comparisons of mean corpuscular volume (MCV), mean blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels between any two of three groups of subjects including 36 oral lichen planus (OLP) patients with macrocytosis (macrocytosis/OLP patients, MCV ≥100 fL), 588 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			
Macrocytosis/OLP patients (n = 36)	103.1 ± 3.2	13.6 ± 1.4 (n = 5)	11.8 ± 1.0 (n = 31)	80.2 ± 20.1 (n = 5)	86.3 ± 21.0 (n = 31)	200.5 ± 103.8	13.3 ± 5.6	16.0 ± 3.5
[a]*P*-value	<0.001	<0.001	<0.001	0.067	0.039	<0.001	0.159	<0.001
[b]*P*-value	<0.001	0.147	<0.001	0.258	0.527	<0.001	0.571	<0.001
[c]OLP patients (n = 588)	88.4 ± 8.5	14.6 ± 1.5 (n = 110)	12.7 ± 1.3 (n = 478)	99.1 ± 36.8 (n = 110)	82.8 ± 30.3 (n = 478)	572.9 ± 258.8	12.7 ± 6.2	9.3 ± 3.6
[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 36 macrocytosis/OLP patients and 588 healthy control subjects by Student's *t*-test.
[b] Comparisons of means of parameters between 36 macrocytosis/OLP patients and 588 OLP patients by Student's *t*-test.
[c] The blood examination data of 588 OLP patients and 588 healthy control subjects were retrieved from our previous study.[14]

Table 2 Comparisons of frequencies of blood hemoglobin and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity between any two of three groups of subjects including 36 oral lichen planus (OLP) patients with macrocytosis (macrocytosis/OLP patients, MCV ≥100 fL), 588 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)	Hyperhomocysteinemia (>12.0 μM)	GPCA positivity
Macrocytosis/OLP patients (n = 36)	24 (66.7)	3 (8.3)	33 (91.7)	0 (0)	34 (94.4)	29 (80.6)
[a]*P*-value	<0.001	<0.001	<0.001	NA	<0.001	<0.001
[b]*P*-value	<0.001	0.268	<0.001	0.875	<0.001	<0.001
[c]OLP patients (n = 588)	148 (25.2)	99 (16.8)	60 (10.2)	7 (1.2)	124 (21.1)	139 (23.6)
[c]Healthy control subjects (n = 588)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.7)	10 (1.7)

NA = not assessed.
[a] Comparisons of frequencies of parameters between 36 macrocytosis/OLP patients and 588 healthy control subjects by chi-square test.
[b] Comparisons of frequencies of parameters between 36 macrocytosis/OLP patients and 588 OLP patients by chi-square test.
[c] The blood examination data of 588 OLP patients and 588 healthy control subjects were retrieved from our previous study.[14]

anemic macrocytosis/OLP patients, 22 (91.7 %) had vitamin B12 deficiency, 2 (8.3 %) had serum iron deficiency, and none had folic acid deficiency, indicating that vitamin B12 deficiency (91.7 %) is the main etiologic factor causing anemia in these 24 anemic macrocytosis/OLP patients.[9] On the contrary, the iron deficiency (8.3 %) is only a minor etiologic factor causing anemia in these 24 anemic macrocytosis/OLP patients. For the 22 vitamin B12-deficient macrocytosis/OLP patients, 17 (77.3 %) were GPCA-positive; thus, the serum GPCA positivity was the predominant factor causing vitamin B12 deficiency in these 22 vitamin B12-deficient macrocytosis/OLP patients.[10,11]

Of the 34 hyperhomocysteinemic macrocytosis/OLP patients, 32 (94.1 %) had vitamin B12 deficiency, 28 (82.4 %) had GPCA positivity, and none had folic acid deficiency, suggesting that GPCA-induced vitamin B12 deficiency is the major contributing factor for hyperhomocysteinemia in these 34 hyperhomocysteinemic macrocytosis/OLP patients.[19]

Moreover, of 29 GPCA-positive macrocytosis/OLP patients, 19 (65.5 %) had both anemia and macrocytosis, 27 (93.1 %) had serum vitamin B12 deficiency, and 28 (96.6 %) had hyperhomocysteinemia, and 3 (10.3 %) had serum iron deficiency, indicating that serum GPCA positivity plays a major role for anemia, macrocytosis, vitamin B12 deficiency, and hyperhomocysteinemia in these 29 GPCA-positive macrocytosis/OLP patients and plays a minor role in causing serum iron deficiency in these 29 GPCA-positive macrocytosis/OLP patients.[10,11]

PA patients should have anemia, macrocytosis, serum vitamin B12 deficiency, and serum GPCA positivity by our definition.[6–8] In this study, the vitamin B12 deficiency was the major contributing factor for hyperhomocysteinemia.[19] Therefore, it is interesting to know the cross-relationship among anemia, serum vitamin B12 deficiency, serum GPCA positivity, and hyperhomocysteinemia in these 17 macrocytosis/OLP patients with PA. In this study, 17 macrocytosis/OLP patients with PA all had anemia, serum vitamin B12 deficiency, serum GPCA positivity, and hyperhomocysteinemia. However, PA (17 macrocytosis/OLP patients with PA) was identified in 70.8 % of 24 anemic, 51.5 % of 33 serum vitamin B12-deficient, 50.0 % of 34 hyperhomocysteinemic, and 58.6 % of 29 serum GPCA-positive macrocytosis/OLP patients.

For the proportions of PA patients in a large group of the patients with oral mucosal diseases such as OLP, AG, or BMS, our previous studies found 17 (2.9 %) PA patients in 588 OLP patients, 22 (2.1 %) PA patients in 1064 AG patients, and 15 (1.7 %) PA patients in 884 BMS patients, suggesting that there is a slightly higher ratio of PA patients in OLP patients.[14,21,25] In more details, for 588 OLP patients, PA is discovered in 47.2 % of 36 macrocytic, 11.5 % of 148 anemic, 28.3 % of 60 serum vitamin B12-deficient, 13.7 % of 124 hyperhomocysteinemic, and 12.2 % of 139 serum GPCA-positive OLP patients.[14] Regarding 1064 AG patients, PA is demonstrated in 53.7 % of 41 macrocytic, 10.9 % of 202 anemic, 39.3 % of 56 serum vitamin B12-deficient, 17.3 % of 127 hyperhomocysteinemic, and 7.8 % of 284 serum GPCA-positive AG patients.[21] For 884 BMS patients, PA is identified in 32.6 % of 46 macrocytic, 8.6 % of 175 anemic, 35.7 % of 42 serum vitamin B12-deficient, 8.8 % of 170 hyperhomocysteinemic, and 13.8 % of 109 serum GPCA-positive BMS patients.[25] Taken these findings together, for overall OLP, AG, and BMS patients, PA was detected in 32.6 %–53.7 % of macrocytic patients, in 8.6 %–11.5 % of anemic patients, in 28.3 %–39.3 % of serum vitamin B12-deficient patients, in 8.8 %–17.3 % of hyperhomocysteinemic, and in 7.8 %–13.8 % of serum GPCA-positive OLP, AG, and BMS patients of a relatively large patients' numbers.[14,21,25]

We found that 66.7 %, 8.3 %, 91.7 %, 0.0 %, 94.4 %, and 80.6 % of 36 macrocytosis/OLP patients were diagnosed as having blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, these 36 macrocytosis/OLP patients had significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 588 healthy control subjects or 588 OLP patients (all P-values <0.001). In addition, 36 macrocytosis/OLP patients also had a significantly higher frequency of serum iron deficiency than 588 healthy control subjects ($P < 0.001$). We conclude that there are significantly higher frequencies of anemia, serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity in macrocytosis/OLP patients than in healthy control subjects. The macrocytosis/OLP patients also have significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than overall OLP patients.[14]

Declaration of competing interest

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

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None.

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