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Original Article

Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with macrocytosis

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KEYWORDS
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Abstract *Background/purpose:* Macrocytosis is defined as having the mean corpuscular volume (MCV) $\geq$ 100 fL. This study evaluated whether 46 burning mouth syndrome (BMS) patients with macrocytosis had significantly higher frequencies of anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity than 442 healthy control subjects or 884 BMS patients.

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deficiency;
Hypehomo
cysteinemia;
Macrocytosis

Materials and methods: Complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 46 BMS patients with macrocytosis, 884 BMS patients, and 442 healthy control subjects were measured and compared.
Results: We found that 65.2%, 23.9%, 47.8%, 0.0%, 60.9%, and 45.7% of 46 BMS patients with macrocytosis were diagnosed as having blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 46 BMS patients with macrocytosis had significantly higher frequencies of blood hemoglobin and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects or 884 BMS patients (all *P*-values < 0.001). In addition, 46 BMS patients with macrocytosis also had a significantly higher frequency of serum iron deficiency than 442 healthy control subjects ($P < 0.001$). Pernicious anemia was found in 15 BMS patients with macrocytosis.
Conclusion: There are significantly higher frequencies of anemia and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity in BMS patients with macrocytosis than in healthy control subjects. BMS patients with macrocytosis also have significantly higher frequencies of anemia, serum vitamin B12 deficiency, hyperhomocysteinemia, and serum GPCA positivity than BMS patients.

Introduction

According to the World Health Organization (WHO) criteria, macrocytosis of erythrocyte was defined as having an MCV $\geq$ 100 fL.[1–3] The etiologies of macrocytic anemia include nutritional deficiencies (vitamin B12 and/or folic acid deficiencies), administration of drugs (e.g., chemotherapeutic, antiretroviral and antimicrobial agents), primary bone marrow disorders (e.g., myelodysplasia and leukemia), and other chronic illness (such as alcoholism and hypothyroidism).[1–3] However, the most common etiology for macrocytic anemia is vitamin B12 deficiency and the patients with macrocytosis may or may not have macrocytic anemia.[1–3] Causes of vitamin B12 deficiency include insufficient intake of vitamin B12, food-bound vitamin B12 malabsorption, presence of autoantibodies against gastric parietal cells and/or intrinsic factors in the body, ileal malabsorption, biologic competition (including bacterial overgrowth and tapeworm infestation), and defective transport (such as transcobalamin II deficiency).[4] The gastric parietal cells can produce hydrochloric acid and intrinsic factor, which can help the iron absorption from the duodenum and proximal jejunum and vitamin B12 absorption from the terminal ileum, respectively.[4] Severe vitamin B12 deficiency may lead to pernicious anemia (PA). Approximately 85% of PA patients possess gastric parietal cell antibodies (GPCA) that induce destruction of gastric parietal cells and subsequently lead to lack of intrinsic factor production.[5,6] Furthermore, 40%—80% of PA patients have intrinsic factor antibodies that bind to the vitamin B12-binding site of intrinsic factor and in turn result in the vitamin B12 malabsorption.[7,8]

The patients with burning mouth syndrome (BMS), atrophic glossitis, oral lichen planus, recurrent aphthous stomatitis, oral submucous fibrosis, or oral precancerous lesions are frequently encountered and the patients with Behcet's disease are less commonly seen in our oral mucosal disease clinic.[9–24,25–58] For patients with one of these seven specific diseases, complete blood count, serum iron, vitamin B12, folic acid, homocysteine, GPCA, thyroglobulin antibody, and thyroid microsomal antibody (also known as anti-thyroid peroxidase antibody or anti-TPO antibody) levels are frequently examined to evaluate whether these patients have anemia, hematinic deficiencies, hyperhomocysteinemia, and serum GPCA, thyroglobulin antibody, and thyroid microsomal antibody positivities.[9–58]

Our previous study found blood hemoglobin (Hb), iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in 19.8%, 16.2%, 4.8%, 2.3%, 19.2%, and 12.3% of 884 BMS patients, respectively.[9] In this study, 46 BMS patients with macrocytosis, 884 BMS patients, and 442 healthy control subjects were retrieved from our previous study.[9] Complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and serum GPCA levels in 46 BMS patients with macrocytosis, 884 BMS patients, and 442 healthy control subjects were measured and compared. We tried to find out whether BMS patients with macrocytosis had significantly higher frequencies of anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects or 884 BMS patients. In addition, we also examined how many percentages of macrocytic BMS patients with vitamin B12 deficiency, hyperhomocysteinemia or GPCA positivity might have PA.

Materials and methods

Subjects

In this study, 46 BMS patients (15 men and 31 women, age range 22—85 years, mean age 64.8 $\pm$ 13.8 years) with

Table 1 Comparisons of mean corpuscular volume (MCV), mean blood concentrations of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine between 46 burning mouth syndrome (BMS) patients with macrocytosis (MCV $\geq$ 100 fL) and 442 healthy control subjects or 884 BMS patients.

Group	MCV (fL)	Hb (g/dL)		Iron (μg/dL)		Vitamin B12 (pg/mL)	Folic acid (ng/mL)	Homocysteine (μM)
		Men	Women	Men	Women			
BMS patients with macrocytosis (n = 46)	103.5 ± 5.5	12.9 ± 1.4 (n = 15)	12.1 ± 1.0 (n = 31)	81.4 ± 25.4 (n = 15)	86.5 ± 30.4 (n = 31)	416.8 ± 310.3	15.4 ± 6.3	15.3 ± 9.9
[a]*P*-value	<0.001	<0.001	<0.001	0.002	0.029	<0.001	0.433	<0.001
[b]*P*-value	<0.001	<0.001	<0.001	0.125	0.631	<0.001	0.369	<0.001
[c]BMS patients (n = 884)	89.6 ± 7.3	14.6 ± 1.5 (n = 212)	13.1 ± 1.2 (n = 672)	92.4 ± 26.8 (n = 212)	89.3 ± 31.8 (n = 672)	639.6 ± 268.1	14.4 ± 7.4	9.3 ± 4.3
[c]Healthy control subjects (n = 442)	90.4 ± 3.6	15.1 ± 0.8 (n = 106)	13.5 ± 0.7 (n = 336)	105.2 ± 28.0 (n = 106)	97.8 ± 27.2 (n = 336)	694.2 ± 220.2	14.7 ± 5.7	8.3 ± 2.0

[a] Comparisons of means of parameters between 46 BMS patients with macrocytosis and 442 healthy control subjects by Student's *t*-test.
[b] Comparisons of means of parameters between 46 BMS patients with macrocytosis and 884 BMS patients by Student's *t*-test.
[c] The blood examination data of 884 BMS patients and 442 healthy control subjects were retrieved from our previous study.[9]

macrocytosis (MCV $\geq$ 100 fL) were selected from 884 BMS patients reported in our previous study.[9] Moreover, the blood examination data of 884 BMS patients (212 men and 672 women, age range 18–90 years, mean 56.1 ± 14.5 years) and 442 healthy control subjects (106 men and 336 women, age range 18–90 years, mean 57.5 ± 13.5 years) were also retrieved from the same previous study for comparisons.[9] All the BMS patients and healthy control subjects were seen consecutively, diagnosed, and treated in the Department of Dentistry, National Taiwan University Hospital (NTUH) from July 2007 to July 2017. Patients were diagnosed as having BMS when they complained of burning sensation and other symptoms of the oral mucosa (such as dry mouth, numbness of oral mucosa, and dysfunction of taste) but no apparent clinical oral mucosal abnormality was found.[9] The detailed inclusion and exclusion criteria for our BMS patients and healthy control subjects have been described previously.[9] In addition, none of the BMS patients had taken any prescription medication for BMS at least 3 months before entering the study.

The blood samples were drawn from BMS patients and healthy control subjects for the measurement of complete blood count, serum iron, vitamin B12, folic acid, and homocysteine concentrations, and the serum GPCA positivity.

Table 2 Comparisons of frequencies of blood hemoglobin (Hb), iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity between 46 burning mouth syndrome (BMS) patients with macrocytosis (MCV $\geq$ 100 fL) and 442 healthy control subjects or 884 BMS patients.

Group	Patient number (%)					
	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 (>12.3 μM)	GPCA positivity
BMS patients with macrocytosis (n = 46)	30 (65.2)	11 (23.9)	22 (47.8)	0 (0.0)	28 (60.9)	21 (45.7)
[a]*P*-value	<0.001	<0.001	<0.001	NA	<0.001	<0.001
[b]*P*-value	<0.001	0.241	<0.001	0.610	<0.001	<0.001
[c]BMS patients (n = 884)	175 (19.8)	143 (16.2)	42 (4.8)	20 (2.3)	170 (19.2)	109 (12.3)
[c]Healthy control subjects (n = 442)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.5)	8 (1.8)

NA = not assessed.
[a] Comparisons of frequencies of parameters between 46 BMS patients with macrocytosis and 442 healthy control subjects by chi-square test.
[b] Comparisons of frequencies of parameters between 46 BMS patients with macrocytosis and 884 BMS patients by chi-square test.
[c] The blood examination data of 884 BMS patients and 442 healthy control subjects were retrieved from our previous study.[9]

All BMS patients and healthy control subjects signed the informed consent forms before entering the study. This study was reviewed and approved by the Institutional Review Board at the NTUH (201212066RIND).

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.[9–14]

Determination of serum gastric parietal cell antibody level

The serum GPCA level was detected by the indirect immunofluorescence technique with rat stomach as a substrate as described previously.[9–14] 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 concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine between 46 BMS patients with macrocytosis and 442 healthy control subjects or 884 BMS patients were performed by Student's *t*-test. The differences in frequencies of blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity between 46 BMS patients with macrocytosis and 442 healthy control subjects or 884 BMS patients 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 concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine in 46 BMS patients with macrocytosis, 884 BMS patients, and 442 healthy control subjects are shown in Table 1. Because men usually had higher blood levels of Hb and iron than women, these two mean levels were calculated separately for men and women. We found that 46 BMS patients with macrocytosis had significantly lower mean blood Hb (for men and women) and serum vitamin B12 levels as well as a significantly higher MCV and mean serum homocysteine level than 442 healthy control subjects or 884 BMS patients (all *P*-values < 0.001, Table 1). In addition, 46 BMS patients with macrocytosis also had significantly lower mean serum iron level (for men and women) than 442 healthy control subjects (both *P*-values < 0.05, Table 1).

According to the World Health Organization (WHO) criteria, macrocytosis of erythrocyte was defined as having an MCV ≥ 100 fL,[1–3] and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.[59] Furthermore, patients with the serum iron level < 60 μg/dL,[60] the serum vitamin B12 level < 200 pg/mL,[61] or the folic acid level < 4 ng/mL[62] were defined as having iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level >12.3 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, 65.2%, 23.9%, 47.8%, 0.0%, 60.9%, and 45.7% of 46 BMS patients with macrocytosis were diagnosed as having blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 46 BMS patients with macrocytosis had significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects or 884 BMS patients (all *P*-values < 0.001, Table 2). In addition, 46 BMS patients with macrocytosis also had a significantly higher frequency of serum iron deficiency than 442 healthy control subjects ($P < 0.001$, Table 2).

In this study, BMS patients with PA were defined as having anemia, macrocytosis, vitamin B12 deficiency, and GPCA positivity.[48–50] By this definition, 15 (32.6%) of 46 BMS patients with macrocytosis had PA. In addition, 15 (50.0%) of 30 anemic, 15 (68.2%) of 22 vitamin B12-deficient, 15 (53.6%) of 28 hyperhomocysteinemic, and 15 (71.4%) of 21 GPCA-positive BMS patients with macrocytosis had PA. The other 15 anemic BMS patients with macrocytosis had macrocytic anemia other than PA.[9]

Discussion

This study found significantly higher frequencies of anemia (65.2%), serum iron (23.9%), and vitamin B12 (47.8%) deficiencies, hyperhomocysteinemia (60.9%), and serum GPCA positivity (45.7%) in 46 BMS patients with macrocytosis than in 442 healthy control subjects. These findings suggest that from the nutritional point of view the macrocytosis in BMS patients is attributed majorly to vitamin B12 deficiency, because none of our 46 BMS patients with macrocytosis have folic acid deficiency. Of the 30 anemic BMS patients with macrocytosis, 20 (66.7%) had vitamin B12 deficiency, 10 (33.3%) had iron deficiency, and none had folic acid deficiency, indicating that vitamin B12 deficiency (66.7%) is the main etiologic factor causing anemia in these 30 anemic BMS patients with macrocytosis, followed by the iron deficiency (33.3%). For the 22 vitamin B12-deficient BMS patients with macrocytosis, 17 (77.3%) were GPCA-positive; thus, serum GPCA positivity was the predominant factor causing vitamin B12 deficiency. Of the 28 hyperhomocysteinemic BMS patients with macrocytosis, 21 (75.0%) had vitamin B12 deficiency, 16 (57.1%) had GPCA positivity, and none (0.0%) had folic acid deficiency, suggesting that GPCA-induced vitamin B12 deficiency is the major contributing factor for hyperhomocysteinemia in these 28 hyperhomocysteinemic BMS patients with macrocytosis. Moreover, of 21 GPCA-positive BMS patients with macrocytosis, 19 (90.5%) had both anemia and macrocytosis, 17 (81.0%) had vitamin B12 deficiency, and 16 (76.2%) had hyperhomocysteinemia, and 8 (38.1%) had iron deficiency, indicating that serum GPCA positivity plays a major role for anemia, macrocytosis, vitamin B12 deficiency, and hyperhomocysteinemia in these 21 GPCA-positive BMS

patients with macrocytosis and plays a minor role in causing iron deficiency in these 21 GPCA-positive BMS patients with macrocytosis.

PA patients should have anemia, vitamin B12 deficiency, and GPCA positivity by our definition.[48—50] In this study, vitamin B12 deficiency was the major contributing factor for hyperhomocysteinemia. Therefore, it is interesting to know the cross-relationship among anemia, vitamin B12 deficiency, GPCA positivity, and hyperhomocysteinemia in 15 macrocytic BMS patients with PA. In this study, 15 macrocytic BMS patients with PA all had anemia, vitamin B12 deficiency, GPCA positivity, and hyperhomocysteinemia. However, PA was identified in 50.0% of 30 anemic, 68.2% of 22 vitamin B12-deficient, 53.6% of 28 hyperhomocysteinemic, and 71.4% of 21 GPCA-positive BMS patients with macrocytosis. If we further counted the PA patients in the original population of 884 BMS patients, PA is discovered in 32.6% of 46 macrocytic, 8.6% of 175 anemic, 35.7% of 42 vitamin B12-deficient, 8.8% of 170 hyperhomocysteinemic, and 13.8% of 109 GPCA-positive BMS patients.[9] For PA in patients with other oral mucosal diseases, our previous studies found PA in 73.3% of 30 anemic, 73.3% of 30 vitamin B12-deficient, 66.7% of 33 hyperhomocysteinemic, and 95.7% of 23 GPCA-positive atrophic glossitis patients with macrocytosis;[15] in 53.7% of 41 macrocytic, 10.9% of 202 anemic, 39.3% of 56 vitamin B12-deficient, 17.3% of 127 hyperhomocysteinemic, and 7.7% of 284 GPCA-positive atrophic glossitis patients;[10] in 11.2% of 89 anemic, 100.0% of 10 vitamin B12-deficient, 18.9% of 53 GPCA-positive BMS patients;[16] in 30.8% of 13 macrocytic, 3.7% of 107 anemic, 12.5% of 32 vitamin B12-deficient, 8.7% of 46 GPCA-positive recurrent aphthous stomatitis patients;[31,32] in 50.0% of 2 macrocytic, 5.3% of 19 anemic, 25% of 4 vitamin B12-deficient, 11.1% of 9 GPCA-positive Behcet's disease patients;[37,38] in 7.8% of 77 anemic and 24.0% of 25 vitamin B12-deficient oral lichen planus patients;[18] in 25.0% of 12 macrocytic, 42.9% of 7 anemic, 23.1% of 13 vitamin B12-deficient, and 7.3% of 41 GPCA-positive erosive oral lichen planus patients;[21] in 54.2% of 24 macrocytic, 48.1% of 27 anemic, 48.1% of 27 vitamin B12-deficient, and 14.1% of 92 GPCA-positive erosive oral lichen planus patients with desquamative gingivitis.[22] Taken these findings together, for overall BMS, atrophic glossitis, recurrent aphthous stomatitis, Behcet's disease, and oral lichen planus patients, PA was detected in 30.8%—53.7% of macrocytic patients, 3.7%—11.2% of anemic patients, in 12.5%—100% of vitamin B12-deficient patients, in 7.7%—18.9% of GPCA-positive patients.[10,16,18,31,32,37,38] However, for macrocytic BMS or atrophic glossitis patients and GPCA-positive erosive oral lichen planus patients with or without desquamative gingivitis, PA could be identified in 25.0%—54.2% of macrocytic patients, in 42.9%—73.3% of anemic patients, in 23.1%—73.3% of vitamin B12-deficient patients, and in 7.3%—95.7% of GPCA-positive patients.[15,21,22]

We found that 65.2%, 23.9%, 47.8%, 0.0%, 60.9%, and 45.7% of 46 BMS patients with macrocytosis were diagnosed as having blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, 46 BMS patients with macrocytosis had significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects or 884 BMS patients (all P-values < 0.001). In addition, 46 BMS patients with macrocytosis also had a significantly higher frequency of serum iron deficiency than 442 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 BMS patients with macrocytosis than in healthy control subjects. BMS patients with macrocytosis also have significantly higher frequencies of blood Hb and serum vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than overall BMS patients.[9]

Declaration of competing interest

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

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