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Original Article

Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with or without microcytosis

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KEYWORDS

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Abstract *Background/purpose:* Microcytosis is defined as having mean corpuscular volume <80 fL. This study evaluated whether 68 burning mouth syndrome (BMS) patients with microcytosis and 816 BMS patients without microcytosis had higher frequencies of anemia, hematinic

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Microcytosis

deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity than 442 healthy control subjects.

Materials and methods: Complete blood count and serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 68 BMS patients with microcytosis, 816 BMS patients without microcytosis, and 442 healthy control subjects were measured and compared.

Results: We found that 73.5%, 44.1%, 4.4%, 2.9%, 13.2%, and 10.3% of 68 BMS patients with microcytosis and 15.3%, 13.8%, 4.8%, 2.2%, 19.7%, and 12.5% of 816 BMS patients without microcytosis had blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Both 68 BMS patients with microcytosis and 816 BMS patients without microcytosis had significantly higher frequencies of blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects (all P -values < 0.05). Moreover, 68 BMS patients with microcytosis had significantly higher frequencies of blood hemoglobin and iron deficiencies than 816 BMS patients without microcytosis.

Conclusion: There are significantly higher frequencies of anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in BMS patients with or without microcytosis than in healthy control subjects. BMS patients with microcytosis have significantly higher frequencies of blood hemoglobin and iron deficiencies than BMS patients without microcytosis.

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Introduction

Microcytosis is defined as having mean corpuscular volume (MCV) < 80 fL. Microcytosis is caused by deficiency of hemoglobin (Hb) structure components including heme (consisted of iron and protoporphyrin IX), α -globin, and β -globin.^{1,2} Iron deficiency may cause iron deficiency anemia (IDA),³ defects in the synthesis of the heme group may result in sideroblastic anemia,² and lack of synthesis of α -globin or β -globin may lead to thalassemia trait-induced anemia.⁴ Because α -globin and β -globin are the two major structural proteins of the Hb and are responsible for maintaining the volume of an erythrocyte, patients with the lack of synthesis of either α -globin or β -globin (such as α -thalassemia or β -thalassemia, respectively) usually have the erythrocytes with the size being smaller than the erythrocytes in patients with either IDA or sideroblastic anemia. Therefore, it is interesting to know whether BMS patients with microcytosis might have significantly higher frequencies of anemia and serum iron deficiency than BMS patients without microcytosis.

Our previous study found that 68 (7.7%), 175 (19.8%), 143 (16.2%), 42 (4.8%), 20 (2.3%), 170 (19.2%), and 109 (12.3%) of 884 BMS patients have microcytosis, blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively.¹ Our findings suggest that not all BMS patients with serum iron deficiency have microcytosis. Other concomitantly-present factors such as serum vitamin B12 and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity may also influence the size of erythrocytes in BMS patients. In this study, the 884 BMS patients were divided into two groups: 68 BMS patients with microcytosis and 816 BMS patients without microcytosis. Complete blood count, serum iron, vitamin B12, folic acid,

homocysteine, and GPCA levels in these 68 BMS patients with microcytosis, 816 BMS patients without microcytosis, and 442 age- and sex-matched healthy control subjects were measured and compared. The major purpose of this study was to assess whether there were significantly higher frequencies of blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in these 68 BMS patients with microcytosis or 816 BMS patients without microcytosis than in 442 healthy control subjects. In addition, we also evaluated whether BMS patients with microcytosis might have significantly higher frequencies of anemia and serum iron deficiency than BMS patients without microcytosis.

Materials and methods

Subjects

This study consisted of 884 BMS patients including 68 BMS patients (11 men and 57 women, age range 18–87 years, mean age 50.2 ± 16.0 years) with microcytosis and 816 BMS patients (201 men and 615 women, age range 18–90 years, mean age 56.6 ± 14.3 years) without microcytosis. For two BMS patients, one age- (± 2 years of each patient's age) and sex-matched healthy control subject was selected. Thus, 442 healthy control subjects (106 men and 336 women, age range 18–90 years, mean 57.5 ± 13.5 years) were selected and included in this study. These 68 BMS patients with microcytosis, 816 BMS patients without microcytosis, and 442 healthy control subjects were retrieved from our previous study.¹ 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 but no apparent clinical oral mucosal abnormality was found.^{1,5–9} The detailed inclusion and exclusion criteria for our BMS patients and healthy control subjects have been described previously.^{1,5–9} In addition, none of the BMS patients had taken any prescription medication for BMS at least 3 months before entering the study. This study was reviewed and approved by the Institutional Review Board at the National Taiwan University Hospital.

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

After obtaining the informed consent forms, the blood samples were drawn from 884 BMS patients and 442 healthy control subjects for determination of complete blood count and serum iron, vitamin B12, folic acid, and homocysteine concentrations by the routine tests performed in the Department of Laboratory Medicine, NTUH.^{1,5–9}

Determination of serum gastric parietal cell antibody level

The serum samples prepared from the blood samples of all BMS patients and healthy control subjects were used for determination of the GPCA level by the indirect immunofluorescence technique with rat stomach as a substrate as described previously.^{1,5–9} Sera were scored as positive when they produced fluorescence at a dilution of 10-fold or more.

Statistical analysis

In this study, the mean corpuscular volume (MCV) and mean blood Hb, iron, vitamin B12, folic acid, and homocysteine concentrations were compared between 68 BMS patients with microcytosis or 816 BMS patients without microcytosis and 442 healthy control subjects as well as between 68 BMS patients with microcytosis and 816 BMS patients without microcytosis 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 68 BMS patients with microcytosis or 816 BMS patients without microcytosis and 442 healthy control subjects as well as between 68 BMS patients with microcytosis and 816 BMS patients without microcytosis were compared by chi-square or Fisher's exact test, where appropriate. 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 68 BMS patients with microcytosis, 816 BMS patients without microcytosis, and 442 healthy control subjects are shown in Table 1. Because men usually had higher mean blood Hb and iron levels than women, these two mean levels were calculated separately for men and women. We found that 68 BMS patients with

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 microcytosis (n = 68)	70.9 ± 5.6	13.2 ± 1.0 (n = 11)	11.5 ± 1.1 (n = 57)	89.6 ± 45.8 (n = 11)	67.5 ± 37.5 (n = 57)	631.1 ± 265.9	11.8 ± 6.5	8.7 ± 3.9
^a <i>P</i> -value	<0.001	<0.001	<0.001	0.103	<0.001	0.033	<0.001	0.190
^b <i>P</i> -value	<0.001	<0.001	<0.001	0.727	<0.001	0.786	0.003	0.266
BMS patients without microcytosis (n = 816)	91.2 ± 4.8	14.7 ± 1.4 (n = 201)	13.2 ± 1.1 (n = 615)	92.5 ± 25.5 (n = 201)	91.3 ± 30.4 (n = 615)	640.3 ± 268.4	14.6 ± 7.4	9.3 ± 4.3
^a <i>P</i> -value	0.002	0.007	<0.001	<0.001	0.001	<0.001	0.805	<0.001
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 68 BMS patients with microcytosis or 816 BMS patients without microcytosis and 442 healthy control subjects by Student's *t*-test.

^b Comparisons of means of parameters between 68 BMS patients with microcytosis and 816 BMS patients without microcytosis by Student's *t*-test.

microcytosis had significantly lower MCV, mean blood Hb (for men and women), iron (for women only), vitamin B12, and folic acid levels than 442 healthy control subjects (all P -values < 0.05 , Table 1). Moreover, 68 BMS patients with microcytosis had a significantly lower MCV, mean blood Hb (for men and women), iron (for women only), and folic acid levels than 816 BMS patients without microcytosis (all P -values < 0.005 , Table 1). Furthermore, 816 BMS patients without microcytosis had significantly lower mean blood Hb (for men and women), iron (for men and women), and vitamin B12 levels as well as significantly higher MCV and mean serum homocysteine level than 442 healthy control subjects (all P -values < 0.01 , Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV < 80 fL,² and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.¹⁰ Furthermore, patients with the serum iron level < 60 μ g/dL,¹¹ the serum vitamin B12 level < 200 pg/mL,¹² or the folic acid level < 4 ng/mL¹³ were defined as having iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level > 12.3 μ M (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations) were defined as having hyperhomocysteinemia. By the above-mentioned definitions, 73.5%, 44.1%, 4.4%, 2.9%, 13.2%, and 10.3% of 68 BMS patients with microcytosis and 15.3%, 13.8%, 4.8%, 2.2%, 19.7%, and 12.5% of 816 BMS patients without microcytosis were diagnosed as having blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. Moreover, both 68 BMS patients with microcytosis and 816 BMS patients without microcytosis had significantly higher frequencies of blood Hb, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects (all P -

values < 0.05 , Table 2). In addition, 68 BMS patients with microcytosis had significantly higher frequencies of blood Hb and iron deficiencies than 816 BMS patients without microcytosis (Table 2).

Fifty BMS patients with microcytosis and 125 BMS patients without microcytosis had anemia (defined as having an Hb concentration < 13 g/dL for men and < 12 g/dL for women).^{1,10} These 175 BMS patients with different types of anemia have been reported previously.¹ In brief, the 50 anemic BMS patients with microcytosis, included 21 with IDA, 27 with thalassemia trait-induced anemia, and two with microcytic anemia other than IDA and thalassemia trait-induced anemia.¹ Moreover, the 125 anemic BMS patients without microcytosis included 15 with pernicious anemia (PA), 15 with macrocytic anemia other than PA, and 95 with normocytic anemia.¹

Discussion

This study found that both 68 BMS patients with microcytosis and 816 BMS patients without microcytosis had significantly higher frequencies of anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects. Moreover, approximately 74% and 44% of 68 BMS patient with microcytosis and approximately 15% and 14% of 816 BMS patient without microcytosis had anemia and serum iron deficiency, respectively. Therefore, BMS patients with microcytosis had significantly higher frequencies of anemia and serum iron deficiency than BMS patients without microcytosis.

Our previous study demonstrated that BMS patient with anemia, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia tend to have atrophic oral epithelium that is easy penetrated by physical and chemical

Table 2 Comparisons of frequencies of blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity between 68 burning mouth syndrome (BMS) patients with microcytosis (MCV < 80 fL) or 816 BMS patients without microcytosis and 442 healthy control subjects as well as between 68 BMS patients with microcytosis and 816 BMS patients without microcytosis.

Group	Patient number (%)					
	Hemoglobin deficiency (Men < 13 g/dL, women < 12 g/dL)	Iron deficiency (< 60 μ g/dL)	Vitamin B12 deficiency (< 200 pg/mL)	Folic acid deficiency (< 4 ng/mL)	Hyperhomocysteinemia (> 12.3 μ M)	GPCA positivity
BMS patients with microcytosis (n = 68)	50 (73.5)	30 (44.1)	3 (4.4)	2 (2.9)	9 (13.2)	7 (10.3)
^a P -value	< 0.001	< 0.001	< 0.001	0.010	< 0.001	< 0.001
^b P -value	< 0.001	< 0.001	0.873	0.974	0.252	0.734
BMS patients without microcytosis (n = 816)	125 (15.3)	113 (13.8)	39 (4.8)	18 (2.2)	161 (19.7)	102 (12.5)
^a P -value	< 0.001	< 0.001	< 0.001	0.004	< 0.001	< 0.001
Healthy control subjects (n = 442)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.5)	8 (1.8)

^a Comparisons of frequencies of parameters between 68 BMS patients with microcytosis or 816 BMS patients without microcytosis and 442 healthy control subjects by chi-square or Fisher's exact test, where appropriate.

^b Comparisons of frequencies of parameters between 68 BMS patients with microcytosis and 816 BMS patients without microcytosis by chi-square or Fisher's exact test, where appropriate.

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

In this study, although 68 BMS patients had microcytosis, only 50 (73.5%) of them had anemia, indicating that not all BMS patients with microcytosis have anemia. Of the 68 BMS patients with microcytosis, 21 (30.9%) had IDA and 27 (39.7%) had thalassemia trait-induced anemia.^{1,3,4} The patients with IDA or thalassemia trait-induced anemia are of no doubt to have microcytosis by definitions.^{3,4} The etiologies of microcytosis in the remaining 20 microcytic BMS patients may need further studies. We suggest that defects in the synthesis of the heme or protoporphyrin IX may be the possible causes resulting in microcytosis in some of the resting 20 microcytic BMS patients.

The group of 816 BMS patients without microcytosis included 770 BMS patients with normocytosis (defined as having MCV between 80 and 99.9 fL) and 46 BMS patients with macrocytosis (defined as having MCV \geq 100 fL).¹ The normocytic anemia is discovered in 95 (12.3%) of 770 BMS patients with normocytosis.¹ Although the normocytic anemia was predominantly associated with chronic diseases, inflammatory diseases, infections, bone marrow hypoplasia, decreased production of erythropoietin or a poor response to erythropoietin, hemolytic disorders, mild but persistent blood loss from gastrointestinal tract, and cytokine-induced suppression of erythropoiesis,^{14–19} deficiencies of iron, vitamin B12, and folic acid were observed in 44.2%, 4.2%, and 7.4% of 95 BMS patients with normocytic anemia.¹ Iron deficiency causes microcytic erythrocytes^{3,10} and deficiencies of vitamin B12 and folic acid lead to macrocytic erythrocytes.^{12,13,20–23} If the anemic patients have concomitant deficiencies of iron, vitamin B12, and folic acid, they may have anemia with normal-sized erythrocytes (normocytic anemia).²³

PA is identified in 15 (32.6%) of 46 BMS patients with macrocytosis.¹ All the 15 PA patients have vitamin B12 deficiency and serum GPCA positivity.^{1,20,21} Moreover, 5 (33.3%) of 15 BMS patients with PA also have serum iron deficiency. Patients with GPCA positivity have a reduced production of intrinsic factor and hydrochloric acid which in turn result in a decreased absorption of vitamin B12 from terminal ileum and a reduced absorption of iron from the stomach and the first part of duodenum, respectively.^{20,21,24} The above-mentioned statement can explain why a relatively high percentage (33.3%) of BMS patient with PA may also have iron deficiency.²⁴

Homocysteine is formed during methionine metabolism.²⁵ Both vitamin B12 and folic acid function as coenzymes for the conversion of homocysteine to methionine.²⁶ Thus, patients with vitamin B12 and/or folic acid deficiencies may have hyperhomocysteinemia.^{1,7,8,25–27} Our previous studies demonstrated that supplementations with vitamin BC capsules plus corresponding deficient vitamin B12 and/or folic

acid can reduce the abnormally high serum homocysteine level to significantly lower levels in patients with either BMS or atrophic glossitis.^{28,29} In this study, hyperhomocysteinemia, vitamin B12 deficiency, and folic acid deficiency were observed in 13.2%, 4.4%, and 2.9% of 68 BMS patients with microcytosis and in 19.7%, 4.8%, and 2.2% of 816 BMS patients without microcytosis, respectively. These data suggest that hyperhomocysteinemia in our BMS patients with or without microcytosis are only partly due to deficiencies of vitamin B12 and/or folic acid. Other factors such as a dysfunction of enzymes and cofactors associated with the process of homocysteine biosynthesis, excessive methionine intake, certain diseases (chronic renal failure, hypothyroidism, PA or sickle cell anemia, and malignant tumors in the breast, ovary, and pancreas), and side effects of some drugs (cholestyramine, metformin, methotrexate, nicotinic acid, fibric acid derivatives, and oral contraceptive pills) may also be considered as the causes resulting in hyperhomocysteinemia in our BMS patients with or without microcytosis.³⁰ Further studies are needed to explore the real etiologies for causing hyperhomocysteinemia in our BMS patients.

The results of this study indicate that there are significantly higher frequencies of anemia, serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity in BMS patients with or without microcytosis than in healthy control subjects. BMS patients with microcytosis have significantly higher frequencies of blood hemoglobin and iron deficiencies than BMS patients without microcytosis.

Declaration of competing interest

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

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