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ORIGINAL ARTICLE

Hematinic deficiencies and anemia statuses in oral mucosal disease patients with folic acid deficiency

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Background/Purpose: Folic acid deficiency (FAD) may result in macrocytic anemia. This study assessed the hematinic deficiencies and anemia statuses in oral mucosal disease patients with FAD (defined as folic acid $\leq$ 6 ng/mL).
Methods: The blood hemoglobin (Hb), iron, vitamin B_{12}, and folic acid concentrations, serum gastric parietal cell antibody level, and mean corpuscular volume (MCV) in 198 oral mucosal disease patients with FAD were measured. Based on World Health Organization (WHO) criteria, anemia or Hb deficiency was defined as having an Hb concentration of $<$13 g/dL for men and $<$12 g/dL for women. In this study, macrocytic anemia due to FAD was defined as having an MCV $\geq$100 fL and folic acid $\leq$6 ng/mL; pernicious anemia as having MCV $\geq$100 fL, vitamin B_{12} $<$ 200 pg/mL, and serum gastric parietal cell antibody positivity; iron deficiency anemia as having MCV $<$80 fL and iron $<$60 μg/dL; and thalassemia trait as having MCV $<$74 fL, red blood cell (RBC) count $>$ 5.0 $\times$ 10^{12}/L, and Mentzer index (MCV/RBC) $<$ 13.
Results: We found that by WHO definitions, 73 (36.9%), 41 (20.7%), and 10 (5.1%) of our 198 FAD patients had concomitant Hb, iron, and vitamin B_{12} deficiencies, respectively. Of 73 anemic FAD patients, three had macrocytic anemia due to FAD, one had pernicious anemia, 14 had iron deficiency anemia, eight had thalassemia trait, and the resting 47 had normocytic anemia.
Conclusion: In addition to macrocytic anemia (2.0%), FAD patients may have concomitant normocytic (23.7%) or microcytic (11.1%) anemia.

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

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Introduction

Folic acid is an important B vitamin that is necessary for DNA synthesis of red blood cells (RBCs). Folic acid deficiency (FAD) may result in macrocytosis that is defined as having a mean corpuscular volume (MCV) $\geq$ 100 fL.[1–3] Patients with FAD or macrocytosis may or may not have anemia. FAD results from poor nutritional intake, malabsorption, hepatobiliary dysfunction, increased folate catabolism, and medication (e.g., methotrexate, 5-fluorouracil, phenytoin).[2] Moreover, the etiologies of macrocytic anemia include nutritional deficiencies (vitamin B_{12} and folic acid), 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] Because multiple causes are involved in FAD and macrocytosis, it is interesting to know the frequency of macrocytosis or macrocytic anemia in oral mucosal disease patients with FAD.

In our oral mucosal disease clinic, there are many patients with burning mouth syndrome (BMS), atrophic glossitis (AG), recurrent aphthous ulcerations (RAUs), or oral lichen planus (OLP). For these patients, complete blood count and examination of serum iron, vitamin B_{12}, folic acid, and homocysteine levels are usually ordered to check whether these patients have microcytic, normocytic, or macrocytic anemia, thalassemia, and deficiencies of hematinics.[4–16] If patients with oral mucosal disease have hematinic deficiencies, multiple hematinic supplement therapy frequently results in correction of anemic status and improvement of oral symptoms and signs.[15,16] Although not often encountered, patients with FAD (defined as having a serum folic acid level $\leq$ 6 ng/mL in this study) sometimes show up at our clinic. In this study, 198 oral mucosal disease patients with FAD were enrolled from the oral mucosal disease clinic of National Taiwan University Hospital (NTUH). Their oral manifestations (including burning sensation and numbness of oral mucosa, dry mouth, dysfunction of taste), specific oral mucosal diseases (such as BMS, AG, RAU, and OLP), MCV, and blood levels of hemoglobin (Hb), iron, vitamin B_{12}, folic acid, and homocysteine were inquired, examined, and recorded. These data were compared with the corresponding data of 198 age- and sex-matched healthy control participants without oral mucosal and systemic diseases to observe the frequencies of FAD in different types of patients with BMS, RAU, AG, or OLP and to assess whether FAD patients had higher frequencies of anemia, other hematinic deficiencies, abnormally high blood homocysteine level, high MCV ($\geq$100 fL), low MCV ($<$80 fL), gastric parietal cell antibody (GPCA) positivity, and specific oral manifestations compared with healthy control participants.

Materials and methods

Patients

In this study, oral mucosal disease patients with FAD were defined as having a serum folic acid $\leq$6 ng/mL. This folic acid concentration was chosen because it was the cutoff point concentration for giving folic acid supplement treatment to FAD patients in our previous studies.[15,16] Based on the above selected concentration for FAD, 198 oral mucosal disease patients (80 men and 118 women, age range 21—85 years, mean 54.5 $\pm$ 14.1 years) with FAD were recruited. For each patient, one age- ($\pm$2 years of each patient's age) and sex-matched healthy control participant was selected. Thus, the normal control group consisted of 198 healthy control participants (80 men and 118 women, age range 20—84 years, mean 55.6 $\pm$ 13.6 years). All the patients and healthy control participants were seen consecutively, diagnosed, treated, and selected in the oral mucosal disease clinic of NTUH from July 2007 to March 2015. The 198 oral mucosal disease patients with FAD had one or two of the oral diseases including BMS, AG, RAU, and OLP. BMS was diagnosed when patients had a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.[4,15] Patients were diagnosed as having partial or complete AG when their dorsal tongues showed partial or complete absence or flattening of filiform papillae, respectively.[5,16] RAU was diagnosed when patients had at least one episode of oral ulcerations per month during the preceding years.[6] OLP was diagnosed according to the following criteria: (1) a typical clinical presentation of radiating grayish-white Wickham striae or papules (nonerosive OLP) combined with erosion or ulceration on the bilateral buccal or vestibular mucosa (erosive OLP); and (2) biopsy specimens characteristic 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.[7,8] However, all FAD 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 FAD patients with serum creatinine concentrations indicative of renal dysfunction (i.e., men, $>$131μM; women, $>$115μM), and who reported a history of stroke, heavy alcohol use, or diseases of the liver, kidney, or coronary arteries were also excluded.[17] Healthy control participants had either dental caries, pulpal disease, malocclusion, or missing teeth but did not have any oral mucosal or systemic diseases. None of our FAD patients had taken any prescription medication for malignancies, epilepsy, diabetes mellitus, infection, inflammation, BMS, AG, RAU, or OLP at least 3 months prior to entering the study.

According to the aforementioned diagnostic criteria, 198 oral mucosal disease patients with FAD retrieved from 77 of 847 BMS patients, 62 of 826 AG patients, 33 (8 also had AG and 4 also had BMS) of 306 RAU patients, and 26 (9 also had AG) of 336 OLP patients were included in this study. For all FAD patients and healthy control participants, oral manifestations including burning sensation and numbness of oral mucosa, dry mouth, dysfunction of taste, AG, RAU, and OLP were inquired, examined, and recorded. The blood samples were drawn from all patients and healthy control participants for measurement of complete blood count, blood iron, vitamin B_{12}, folic acid, and homocysteine concentrations as well as serum GPCA levels. All patients and healthy control participants signed an informed consent form prior