Oral Manifestations of Vitamin B_{12} Deficiency: A Case Report

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SOMMAIRE

Les anémies mégaloblastiques forment un sous-groupe d'anémies macrocytaires qui se caractérisent par une anomalie morphologique particulière dans les précurseurs des globules rouges dans la moelle osseuse, en l'occurrence une dysérythropoïèse. Parmi les nombreuses causes de l'anémie mégaloblastique, les plus répandues sont les troubles dus à une carence en cobalamine ou en folates. Les symptômes cliniques incluent faiblesse, fatigue, essoufflement et anomalies neurologiques. La manifestation de signes et symptômes buccaux – y compris la glossite, la chéilite angulaire, des ulcérations buccales récurrentes, la candidose buccale, l'inflammation érythémateuse diffuse de la muqueuse et la pâleur de la muqueuse buccale – offre au dentiste la possibilité de participer au diagnostic de cette affection. Un diagnostic précoce est important pour prévenir les signes neurologiques qui peuvent être irréversibles. Cet article décrit les changements buccaux observés chez un patient atteint d'anémie mégaloblastique due à une carence alimentaire en cobalamine.

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Megaloblastic anemias are a subgroup of macrocytic anemias caused by impaired DNA synthesis that results in macrocytic red blood cells, abnormalities in leukocytes and platelets and epithelial changes, particularly in the rapidly dividing epithelial cells of the mouth and gastrointestinal tract. The most common causes of megaloblastic anemias are cobalamin (vitamin B_{12}) and folate (vitamin B_9) deficiency.[1-3]

Clinically, megaloblastic anemia progresses slowly, and symptoms include weakness, fatigue, shortness of breath and neurologic abnormalities. Oral signs and symptoms, including glossitis, angular cheilitis, recurrent oral ulcer, oral candidiasis, diffuse erythematous mucositis and pale oral mucosa,[4,5] offer the dentist an opportunity to participate in the diagnosis of this condition.

The objective of this paper is to report a case of megaloblastic anemia in which oral manifestations were significant and to review the literature regarding symptoms, diagnostic methods and treatment.

Case Report

In March 2005, a 41-year-old woman was referred by her general dentist to the surgery and buccal pathology service at João de Barros Barreto University Hospital. Her chief complaint

was difficulty in eating certain types of food (mainly banana and tomato) because of a burning sensation and the presence of red stains on the inside of her cheeks and on her tongue.

She had been a strict vegetarian for 2.5 years and had not consumed milk, cheese, fish, meat or eggs during that time. She was not taking any medication. The current symptoms had been present for more than a year. Her past medical and dental histories were non-contributory and she reported no history of allergy.

During clinical evaluation, paleness and dry lips were detected. The patient also displayed a disturbance of taste (she was unable to sense the flavour of a variety of fruits and vegetables), fatigue after simple daily activities, paresthesia of the anatomic structures innervated by the mandibular division of the trigeminal nerve on her left side, disturbance of memory and slowing mental faculty, characterized by forgetting recent facts, dates, appointments and difficulty in answering simple questions, respectively.

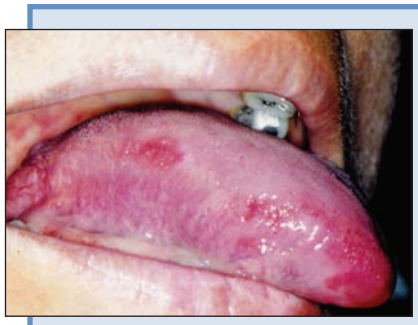

Figure 1a: Papillary atrophy and erythema involving the lateral border of the tongue before treatment.

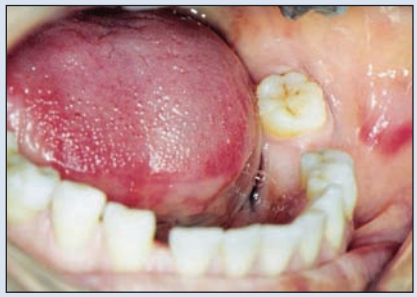

Figure 1b: Erythema involving the mucosa of the cheek and the anterior portion of the tongue.

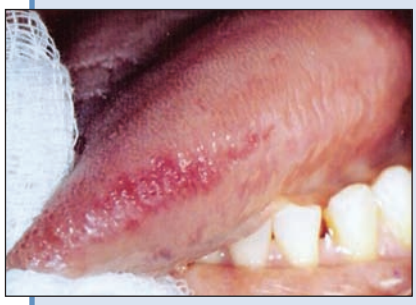

Figure 1c: Well-circumscribed erythematous macules seen on the lateral border of the tongue.

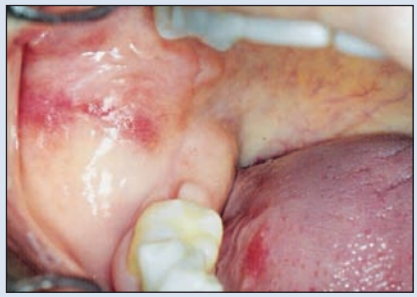

Figure 1d: Erythema involving the mucosa of the right cheek.

Oral examination revealed pale oral mucosa, glossitis with papillary atrophy and multiple areas of painful erythema on the dorsal surface and lateral borders of the tongue and buccal mucosa (**Figs. 1a** and **1b**). The mucosa covering the lesions appeared atrophic, but no frank ulceration was evident (**Figs. 1c** and **1d**).

Hematologic tests were done (**Table 1**). Neutrophil nuclei were hypersegmented, with more than 5 lobes. Anti-intrinsic factor antibodies were not detected, therefore it was not necessary to perform the Schilling test.

A diagnosis of megaloblastic anemia was made based on the high levels of mean corpuscule volume and red cell distribution width, neutrophil hypersegmentation and cobalamin deficiency, and the patient was referred to a centre for hemotherapy and hematology. Treatment comprised parenteral doses of cobalamin (1,000 mg/week hydroxocobalamin administered intramuscularly over 30 days) and 1 mg of folic acid daily for 30 days. Blood cell counts were repeated monthly. The patient was asked to modify her diet and to add beef liver daily. She returned weekly to the surgery and buccal pathology service for evaluation of her oral lesions, which began to diminish during the first week of therapy. After 14 days of treatment, the lesions had completely disappeared, as had all other symptoms (**Figs. 2a–2d**).

Table 1 Comparison of patient's hematologic test results with normal values

Test	Normal range (female)	Patient's values
RBC count (cells/μL)	3.90–5.03	1.63
Hemoglobin (g/dL)	12.0–15.5	7.2
MCV (fL)	80–100	144
Hematocrit (%)	36–45	23.4
RDW (%)	13±1.5	25
Serum folate (ng/mL)	3–16	7.73
Serum cobalamin (pmol/L)	118–716	71.8

MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width.

Discussion

Vitamin B_{12} is found only in bacteria, eggs and foods of animal origin. It does not occur in vegetables and fruit. The average daily requirement for cobalamin in adults is 1–2 μg.[6] Most cobalamin in food is bound to proteins and released when the protein is subjected to acid-peptic digestion in the stomach. The released cobalamin rapidly attaches to a cobalamin-binding protein, R-binder, present

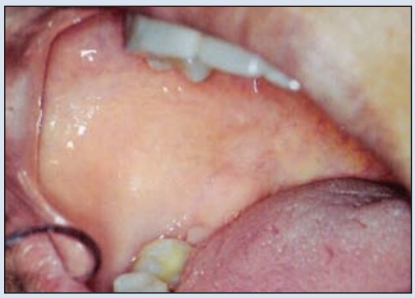

Figure 2a: Dramatic resolution of erythema and all pathologic symptoms after 1 week of treatment with parenteral doses of cobalamin and folic acid.

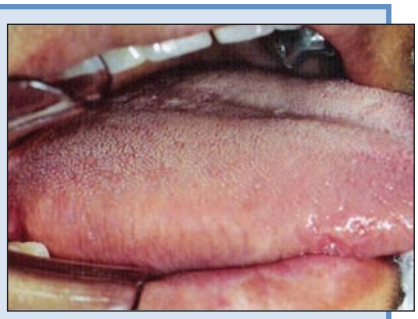

Figure 2b: Absence of papillary atrophy and erythema previously seen on the lateral border of the tongue.

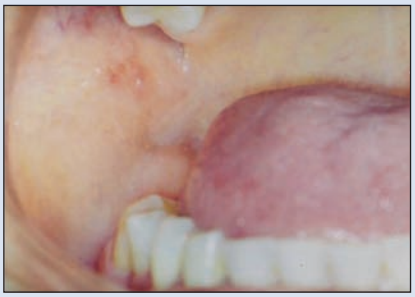

Figure 2c: Tissue regeneration on the mucosa of the cheek appeared complete after 2 weeks of treatment.

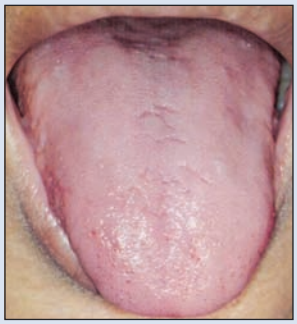

Figure 2d: Complete tissue regeneration on the tongue after treatment.

in saliva and gastric juice. The R-binder in the R-binder complex is broken down in the alkaline environment of the jejunum by pancreatic trypsin and the released cobalamin binds to intrinsic factor produced by gastric parietal cells in the duodenum and is transported to the distal ileum, where specific receptors bind the B_{12}-intrinsic factor complex resulting in B_{12} absorption. This attachment is calcium dependent, the calcium being provided by the pancreas. In the absence of intrinsic factor, cobalamin is absorbed only very inefficiently by passive diffusion. Most cobalamin is stored in the liver (about 4–5 mg). Megaloblastic anemia occurs when the body's cobalamin stores fall below 0.1 mg.[1,3,6-8]

Macrocytosis due to cobalamin or folate deficiency is a direct result of ineffective or dysplastic erythropoiesis. These vitamins are the most important cofactors necessary for normal maturation of all cells and cobalamin is necessary for DNA synthesis, as its deficiency prevents cell division in the marrow.[4,9] When either of these factors is deficient, red blood cells (RBCs) become large erythroblasts with nuclear or cytoplasmic asynchrony (poikilocytosis), a characteristic of all megaloblastic anemias.[4,10]

Dentists' involvement in the diagnosis of this condition is based on changes in oral mucous membranes, which have been reported in 50%–60% of all patients with megaloblastic anemia.[3,11] These oral changes may occur in the absence of symptomatic anemia or macrocytosis, as they may precede many systemic indicators of B_{12} deficiency.[4,12,13] Thus, the general dentist, who is cognizant of normal blood values and can interpret anomalies, may order specific blood tests before the patient is referred to a hematologist. However, patients must be referred to a hematologic centre for adequate treatment.

A wide range of oral signs and symptoms may appear in anemic patients as a result of basic changes in the metabolism of oral epithelial cells. These changes give rise to abnormalities in cell structure and the keratinization pattern of the oral epithelium leading to a "beefy" red and inflamed tongue with erythematous macular lesions on the dorsal and border surfaces because of marked epithelial atrophy and reduced thickness of the epithelial layer. In the case described above, for example, erythematous macules occurred on the surface of the patient's cheek mucosa and tongue. In addition, soreness of the tongue and generalized ulceration, as well as reduced taste sensitivity, generalized sore mouth or burning mouth are usually reported in the literature and were also present in the current case.[3,11] Although candidiasis and angular cheilitis are common oral complaints of patients with megaloblastic anemia, these problems were not observed in our patient. The differential diagnosis of patients with these signs and symptoms includes iron deficiency, diabetes, allergy, autoimmune disease, physical and chemical injury, atrophic candidiasis and anemia of chronic disease.[4,11,14]

Megaloblastic anemia develops slowly and takes 2–5 years to develop, as the body stores relatively large amounts of vitamin B_{12} in comparison with daily requirements.[4,8] This timeframe is consistent with our clinical case, as the patient reported that she had been a strict vegetarian for more than 2 years.

Although vitamin B_{12} deficiency is almost always associated with people who are strict vegetarians, the condition also results from malabsorption of the vitamin, which can occur secondary to inadequate gastric production or defective functioning of intrinsic factor. Other conditions that can lead to vitamin B_{12} deficiency include gastrectomy, bacterial overgrowth in the small intestine, diverticulitis, celiac disease, Crohn's disease, alcoholism, HIV and medications such as neomycin and colchicine. In addition, malabsorption of dietary protein-bound vitamin B_{12} has been associated with the use of H_2-receptor antagonists

and long-term use of proton-pump inhibitors, such as omeprazole, normally prescribed for gastroesophageal reflux disease. Malabsorption of dietary vitamin B_{12} is thought to be a result of its impaired release from food protein, which requires gastric acid and pepsin as the initial step in the absorption process. Thus, according to some reports[15-18] prolonged use of H_2-receptor antagonists or proton-pump inhibitors could contribute to the development of vitamin B_{12} deficiency. Patients taking these medications for extended periods, particularly >4 years, should be monitored for vitamin B_{12} status.

Careful investigation of clinical history and clinical examination are very helpful in determining the cause of megaloblastic anemia. In fact, the patient's history often immediately reveals the cause. Mean corpuscular volume, RBC, hemoglobin level, blood film and levels of serum folate, red cell folate and serum B_{12} are the primary investigations. Also of use are tests for serum/plasma methylmalonic acid and plasma total homocysteine, which are both substrates of cobalamin, and serum holo-transcobalamin II, a metabolically active protein that transports cobalamin to cell membrane receptors. An increase in the levels of these metabolites usually precedes the development of hematologic abnormalities and, thus, can signal this disorder in the absence of hematologic abnormalities.[1,4,9,13,19,20] Definitive diagnosis of pernicious anemia, however, is made using the Schilling test to investigate intrinsic factor.[4,11]

When serum cobalamin levels are assessed, folate levels must be assayed at the same time to explore the possibility that the primary deficiency may be of folate rather than cobalamin.[1] However, serum folate levels tend to be increased in patients with cobalamin deficiency, presumably because of impairment of the methionine synthase pathway and accumulation of methyltetrahydrofolate, the principal form of folate in serum. On the other hand, low RBC folate levels are seen in patients with cobalamin deficiency. Approximately 60% of patients with pernicious anemia have low RBC folate levels, presumably because cobalamin is necessary for normal transfer of methyltetrahydrofolate from plasma to RBCs.[9] In our patient, RBC folate level was not investigated. In this situation, Aslinia and colleagues[9] recommend that patients receiving treatment for cobalamin deficiency should also receive folate supplementation at the rate of 400 µg/day to 1 mg/day. Thus, folate was administered to our patient.

Cobalamin deficiency is usually treated by parenteral administration of cyanocobalamin (intramuscularly or subcutaneously, 1000 µg/week for 1 month and monthly thereafter) or hydroxocobalamin in the same dose every 1–3 months intramuscularly. Intramuscular administration has been used for years and, in the current case, this method was chosen because of the patient's cognitive and neurologic impairment. However, sublingual and oral administration of cobalamin are equally effective.[9,20] Liver is recommended as a dietary supplement because beef liver contains about 110 µg of cobalamin and about 140 µg of folate per 100 g.[6] An optimal response to therapeutic doses of cobalamin confirms the diagnosis of cobalamin deficiency. A suboptimal response may indicate that the initial diagnosis was wrong, but is more often a result of coexisting iron deficiency, infection, chronic inflammatory disorder, renal failure or the use of drugs such as cotrimoxazole (combination of trimethoprim and sulfamethoxazole, a sulfa drug).[1]

In conclusion, megaloblastic anemia has a complex pathogenesis. As oral lesions are among the most common initial symptoms,[11] the dentist, who is often consulted first, has a prime opportunity and responsibility to contribute to diagnosis.

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