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Difficulties in the diagnosis of Biermer's disease – a case report

Trudności diagnostyczne choroby Biermera – opis przypadku

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Abstract

Biermer's disease (pernicious anemia PA), is an autoimmune disease inducing vitamin B12 deficiency by malabsorption. The clinical presentation of Biermer's disease (pernicious anemia), is often insidious because the onset is difficult to establish and progression is very slow. It rarely occurs before the age of 30, the mean age at which it is diagnosed being about 60. Patients may seek medical advice due to non-specific symptoms such as weakness, decreased mental concentration, and headaches. Biermer's disease may be accompanied by other autoimmune diseases. Longstanding Helicobacter pylori infection probably plays a role in many patients with PA. In this case report a 22-year old woman with Biermer's disease coexisting with Hashimoto thyroiditis and a Helicobacter pylori infection has been described. This case indicates the important role of dentists in the early diagnosis of this disease, especially in respect of later neurological complications.

Keywords: Biermer's disease; vitamin B12; anemia.

Streszczenie

Choroba Biermera (niedokrwistość złośliwa, PA) jest chorobą autoimmunologiczną, spowodowaną obniżeniem poziomu witaminy B12 wynikającym z niedoboru w żołądku czynnika wewnętrznego. Kliniczny przebieg choroby jest często podstępny, ponieważ początkowe objawy są trudne do wykrycia, a postęp powolny. Choroba ta rzadko występuje przed 30. rokiem życia, średni wiek, w którym jest diagnozowana wynosi około 60 lat. Początkowe objawy są niespecyficzne, tj. osłabienie, obniżona zdolność koncentracji, ból głowy. Choroba Biermera może towarzyszyć innym chorobom autoimmunologicznym. Długotrwająca infekcja *Helicobacter pylori* prawdopodobnie odgrywa rolę u wielu pacjentów z PA. W pracy zaprezentowano przypadek 22-letniej kobiety z chorobą Biermera występującą równocześnie z zapaleniem tarczycy Hashimoto oraz infekcją *Helicobacter pylori*. Przypadek ten wskazuje na istotną rolę lekarzy stomatologów we wczesnym rozpoznaniu tej jednostki chorobowej, szczególnie w aspekcie późniejszych powikłań neurologicznych.

Słowa kluczowe: choroba Biermera; witamina B12; niedokrwistość.

Introduction

Biermer's disease (pernicious anemia), is an autoimmune atrophic gastritis inducing vitamin B12 deficiency by malabsorption. Vitamin B12 (B12, cobalamin) deficiency is the most common cause of PA. In cases diagnosed very early, Hb and MCV are within the reference range [1]. PA may coexist with other autoimmune disease; it most often accompanies the Hashimoto disease. Longstanding *Helicobacter pylori (H. pylori)* infection probably plays a role in many patients with PA [2]. Glossitis with linear lesions is thought to be characteristic in B12 deficiency in its early phases [3].

Case report

22-year woman was referred to the Department of Periodontology and Oral Mucosa Diseases in Medical University of Gdańsk. She suffered from dry, sore mouth, tongue hypersensitivity to spicy foods, recurrent oral ulceration for 2-years duration. She complained of dry, rough skin; brittle and coarse hair; tiredness. She denied nutritional deficiency and alcohol abuse.

Over the course of her illness she was treated with local antifungal therapy by her primary care physician with no diagnosis and getting no improvement. Normal blood count, performed by the physician 5 months before coming to our Department, besides CRP 6,3 mg/l, showed no abnormalities.

Oral examination at the day she referred to our Department revealed angular cheilitis; erythematous areas of the tongue some of them with linear pattern in the dorsal surface (**Figure 1**).

Dry, rough skin around nose was observed. The history of the ulcers was characteristic for minor aphthae and no scaring of the mucosa was evident. A cytologic smear of oral mucosa was positive for *Candida*. She was consulted by haematologist, endocrinologist, gastrologist. Blood tests revealed: RBC 5,12 [normal 4,0–5,0 T/l], Hb 15 [normal 12–16 g/dl], MCV 89,5 [normal 80–96 fl], CRP 7,5 [normal < 5,0 mg/l], iron 56 [normal 49–151 ug/dl], ferritin 5,27 [normal 15–250 ng/mL], transferrin 4,99 [normal 2,0–3,6 g/dl], folate > 45 [normal 10–42 nmol/l], vitamin B12 (cobalamin) 42,82 [normal 191–663 pg/ml], TSH 8,08 [normal 0,27–4,2 mIU/l], FT4 16,11 [normal 12–22 pmol/l], FT3 TgAb 16,7 [normal < 115 IU/ml], TPOAb 428,7 [normal < 34 IU/ml], total cholesterol 219 [normal 125–200 mg/dl], ALAT 28 [normal 5–31 U/l], ASPAT 27 [5–31 U/l]. Ultrasonography revealed normal sized, hypoechogenic thyroid. Panendoscopic and histopathologic examination revealed hernia of hiatus esophagus and active chronic gastritis of antrum, partially atrophic with foveolaris regenerative hyperplasia. *Helicobacter pylori* infection was also noticed. The

Table 1. Diagnostic criteria of pernicious anemia [7]

Tabela 1. *Kryteria rozpoznania niedokrwistości złośliwej [7]*

Diagnostic criteria of pernicious anemia:
Hb < 13 g/dl (men), Hb < 12 g/dl (women);
MCV ⩾ 100 fL;
low levels of cobalamin, together with the concomitant presence of atrophic body gastritis (ABG) and intrinsic factor (IF) deficiency.

Table 2. Definitions of cobalamin deficiency [8]

Tabela 2. *Kryteria rozpoznania niedoboru kobalaminy [8]*

Definitions of cobalamin deficiency:
serum cobalamin levels < 150 pmol/L (< 200 pg/mL) with clinical features and/or hematological anomalies related to cobalamin deficiency;
serum cobalamin levels < 150 pmol/L on two separate occasions;
serum cobalamin levels < 150 pmol/L and total serum homocysteine levels < 13 µmol/L or methylmalonic acid levels < 0,4 µmol/L (in the absence of renal failure and folate and vitamin B6 deficiencies);
low serum holotranscobalamin levels < 35 pmol/L.

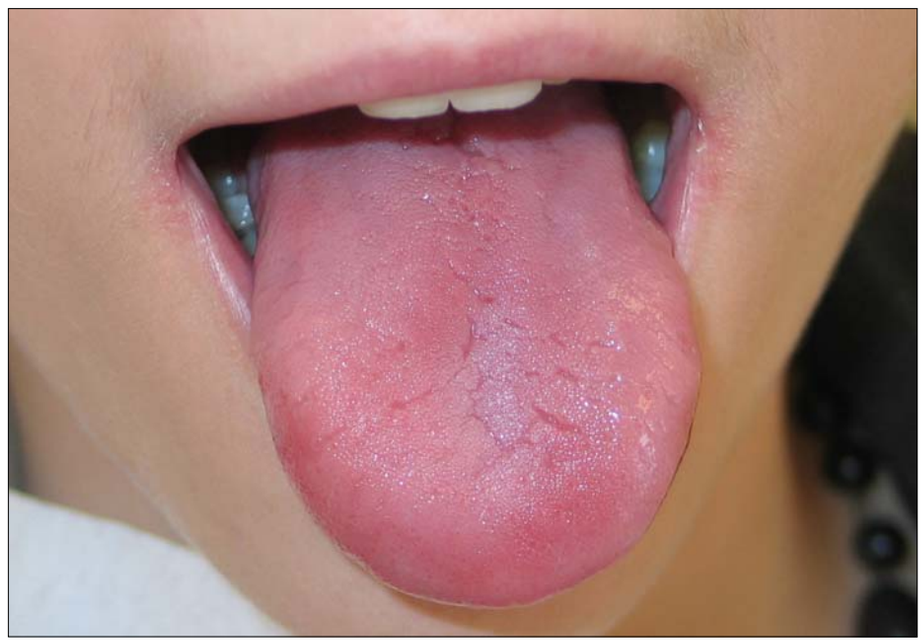

Figure 1. Image of tongue of patient with pernicious anemia

Rycina 1. *Obraz języka u pacjentki z niedokrwistością złośliwą*

diagnosis was: Biermer's disease, Hashimoto thyroiditis, atrophic gastritis, *H. pylori* infection. She was treated with intramuscular vitamin B12 injections, levothyroxine, *H. pylor*i eradication and local antifungal therapy (*Nystatin*). All oral changes improved after 3-weeks of supportive medical therapy.

Discussion

Pernicious anemia is uncommon before the age of 30 (4%), most patients are 50–70 years old [1]**.** The male: female ratio is about 1:1,5. About 25% of patients give a family history of pernicious anemia and 10% have clinical or subclinical autoimmune disease (thyroid diseases, vitiligo, hypoparathyroidism, and hypofunction of the adrenal glands) in both patients and their relatives and, probably, of type I diabetes in patients [1]. Pernicious anemia may occur as a part of the polyendocrinopathy syndrome and then presents in the second decade. Occasional cases of pernicious anemia have hypogammaglobulinaemia or pure red cell aplasia [1].

The clinical presentation of pernicious anemia is often insidious for various reasons. The onset and progression of pernicious anemia are very slow. The underlying disease may not be suspected until a complete red blood count has been performed. Patients with pernicious anemia may seek medical advice due to non-specific symptoms related to the presence of anemia per se, such as weakness, asthenia, decreased mental concentration, headache, cardiological symptoms such as palpitations and chest pain [2]. Less frequently, patients with pernicious anemia may present only with neurological symptoms, such as paresthesia, unsteady gait, clumsiness, and in some cases, spasticity. B12 deficiency may cause peripheral neuropathy and lesions in the posterior and lateral columns of the spinal cord and in the cerebrum, and these lesions progress from demyelinization to axonal degeneration and eventual neuronal death. It is particularly important to recognize these symptoms early, because the neurological lesions may not be reversed after replacement therapy with vitamin B12 [3, 4]. Oral manifestation of cobalamin deficiency have been described as glossitis, erosive glossitis, depapillated erythematous linear lesion affecting tongue [3–5]. Classic Hunter glossitis has two stages: inflammatory in the beginning, with bright red plaques, and atrophic later characterized by papillae atrophy affecting more than 50% of the tongue [6]. Finding of glossitis with linear lesions is characteristic of vitamin B12 deficiency in its early phases [3].

The patient described here showed early oral signs of Biermer's disease such as linear glossitis. Cobalamin was very low (42,82 pg/ml); Hb, MCV, iron were in the reference range, ferritin was low, transferrin was high.

Low serum B12 levels are not specific for B12 deficiency but may also be fund, in the absence of B12 related metabolic abnormalities, in folate deficiency, pregnancy, HIV infection, myeloma, mild or severe transcobalamin. When serum B12 levels are assayed, folate levels must also be assayed at the same time. Many low serum B12 levels remain unexplained. An optimal response to therapeutic doses of B12 confirms the diagnosis of B12 deficiency [1, 7, 8].

About 25–40% of patients with cobalamin-responsive disorders have normal MCVs and a similar percentage are not anaemic. In 15–25% both the Hb and MCV are within the reference range. B12 deficiency should not be excluded on the basis of a normal blood count or a low-normal serum B12 level in a clinical setting suggestive of deficiency, particularly in patients with symptoms consistent with B12 neuropathy [1].

Experimental and clinical data suggest an involvement of long-standing *H. pylori* infection in the pathogenesis of ABG and pernicious anemia [2].

Although pernicious anemia is typically a disease of elderly whites, it is very important to take under consideration management and implications of this disease state in women in childbearing age. There is higher incidence of intrauterine death with severe maternal cobalamin deficiency. Low maternal serum cobalamin levels also have been associated with prematurity [6, 8].

This case reminds that dentists and physicians should be aware of the importance of recognizing oral manifestations to avoid complications associated with Biermer's disease. Furthermore, ase the disease can present subtly, pernicious anemia also must be considered in demographic groups not classically thought to be at risk.

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