

# Chronic pain and vitamin B12 deficiency, a challenging and important differential diagnosis. Case report

*Dor crônica e deficiência de vitamina B12, um diagnóstico diferencial desafiador e importante. Relato de caso*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** The study's objective was to present a case of diffuse chronic pain with 36 months of development, associated with recurrent oral aphthous ulcers and glossitis, highlighting the importance of the wide differential diagnosis and the possibility of vitamin B12 deficiency as a cause.

**CASE REPORT:** Male patient, 39 years-old, white, reported diffuse pain predominantly in the cervical, thoracic, abdominal, thighs and left knee regions, besides the presence of frequent oral aphtae, lasting more than 5 days, multiple and painful, predominantly on the tongue, for 6 months. The condition was attributed to Behçet's disease, but there was complete and permanent remission after treatment with vitamin B12.

**CONCLUSION:** It's important to insert vitamin B12 deficiency for differential diagnosis in chronic pain scenarios.

**Keywords:** Behçet disease, Chronic pain, Glossitis, Oral ulcer, Vitamin B12.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** O objetivo deste estudo foi apresentar um caso de dor crônica difusa com 36 meses de evolução, associada com aftas orais de repetição e glossite, destacando a importância do amplo diagnóstico diferencial e da possibilidade da deficiência de vitamina B12 como causa.

**RELATO DO CASO:** Paciente do sexo masculino, 39 anos, branco, referindo dores difusas que predominavam em região cervical, torácica, abdominal, coxas e joelho esquerdo, além da

presença de aftas orais frequentes, com duração superior a 5 dias, múltiplas e dolorosas, predominando na língua, há 6 meses. O quadro foi atribuído à doença de Behçet, mas houve remissão total e permanente após tratamento com vitamina B12.

**CONCLUSÃO:** É importante prescrever a deficiência de vitamina B12 para o diagnóstico diferencial em quadros de dor crônica.

**Descritores:** Dor crônica, Glossite, Doença de Behçet, Úlcera oral, Vitamina B12.

## INTRODUCTION

Chronic pain (CP) is one of the most important and prevalent symptoms faced by mankind. Etiology is not always defined, and in some cases, it's characterized as idiopathic or without a known cause. There are patients whose CP, even after exhaustive investigation, does not have its cause or anatomical substrate discovered. There are reports in the literature about the use of vitamin B12 in the treatment of some types of CP.

The purpose of the present study was to present a clinical case with predominantly diffuse CP and oral aphtae, which was initially attributed to Behçet's disease, but which had total and permanent remission after the vitamin B12 treatment, evidencing its deficiency as the cause of CP and recurrent oral aphtae.

## CASE REPORT

Male patient, 39 years old, white, referred to Rheumatology with generalized pain lasting for 6 months. The patient reported diffuse pain that predominated in cervical, thoracic, abdominal, thighs and left knee region. Another important finding was the presence of frequent oral aphtae, lasting more than 5 days, multiple and painful, predominantly on the tongue. There was also a history of genital aphtae on the glans, however, less frequently. The patient had no joint manifestations such as arthritis or arthralgia. Physical examination revealed 2 tongue aphtae of 0.5 and 1 cm in diameter and discrete folliculitis-like lesions on the dorsum and face, with no other relevant changes. After laboratory investigation (Table 1), the diagnosis hypothesis of Behçet's disease was made based on the clinical scenario, although there was no ophthalmologic or central nervous system compromise and the pathergy test was negative. Initially, there was a slight improvement in the frequency of aphtae, however, after a few months, there was an accentuation not only of the oral lesions, but also of pain.

The patient abandoned the medical follow-up and started treatment with analgesics and anti-inflammatory drugs with inade-

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quate symptomatic control. He returned after 3 years with worse pain, which predominated in the thoracic, abdominal, upper, and lower limbs regions, oral aphtae with pain in the tongue and a sensation of discomfort and burning, suggesting glossitis (Figure 1). With this information, the diagnostic hypothesis of vitamin B12 deficiency was made, confirmed by the tests in table



**Figure 1.** Smooth tongue with loss of papillae before treatment with vitamin B12

1. Treatment with vitamin B12 (chromoactive cobalamin) was initiated, initially with 5000µg intramuscular every 7 days for one month and then every 30 days, resulting in symptom improvement, with complete remission of pain and tongue alterations after 1 month of treatment (Figure 2). No new oral or genital aphtae occurred after 10 months of treatment.



**Figure 2.** Normal tongue appearance with presence of papillae after treatment with vitamin B12

**Table 1.** Evolution of tests before and after beginning treatment with vitamin B12

Laboratory	Start	At 36 months	After vitamin B12	RV
Hemoglobin (g/dL)	14	12	15	13-17
Leukometry (/mm <sup>3</sup> )	7.400	6300	8500	4.000-10.000
Platelets (mil/mL)	316.000	272.000	280.000	150.000-400.000
RDW (%)	11.8	12.9	14.9	11-15
Ferritin (ng/mL)	-	48.1	-	22-322
MCV (fL)	92.6	101	96.9	81-101
ESR (mm/h)	14	15	-	< 20
CRP (mg/dL)	3	4	-	< 6
ANF	NR	-	-	NR
Vitamin B12 (pg/mL)	-	186	> 2000	211-911
Folic acid (ng/mL)	-	-	12.8	> 3.37
Homocysteine (micromol/L)	-	28.4	16.6	7.7-22.3
25(OH)D (ng/mL)	24.3	21.5	-	> 20
LDH (U/L)	-	278	201	120-246
CK (U/L)	194	198	-	< 200
TSH (micro Ui/mL)	2.55	-	-	0.5-5
T4 (ng/dL)	0.95	-	-	0.89-1.76
AST (U/L)	15	19	20	< 50
ALT (U/L)	16	13	18	< 50
GGT (U/L)	31	-	28	7-58
Homocysteine	0.9	-	0.9	0.7-1.1
Anti-parietal cell AB	-	-	NR	NR
Anti-intrinsic factor AB (UR/mL)	-	-	2	< 20

RV = reference values; Hb = hemoglobin; RDW = red blood cell distribution range; MCV = mean corpuscular volume; ESR = erythrocyte sedimentation rate (after 1 hour); CRP = C-reactive protein; ANF = antinuclear factor; NR = non-reactive; LDH = lactate dehydrogenase; CK = creatine kinase; TSH = thyroid stimulating hormone; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyl transpeptidase; AC = antibody.

Continuing with the etiologic investigation, the researchers verified that the patient had an inadequate diet for some years, with a predominance of carbohydrates. The upper digestive endoscopy showed mild chronic gastritis with a positive test for *Helicobacter pylori*, and he was submitted to treatment with the classical strategy and a negative test for celiac disease. The colonoscopy showed normal results, as was a 4-limb electroneuromyography performed for the ropedeutics of the diffuse pain scenario.

## DISCUSSION

Vitamin deficiencies are a common problem in the world. Recognition and treatment of vitamin B12 deficiency is essential because it's a reversible cause of bone marrow failure and demyelinating diseases.

Vitamin B12 is involved in the conversion of methylmalonyl-CoA (methylmalonic acid bound to coenzyme A) to succinyl-CoA by the enzyme methylmalonyl-CoA mutase with adenosyl-B12 as a cofactor. B12 deficiency causes increased levels of methylmalonic acid in plasma<sup>1</sup>.

The diagnosis of B12 deficiency can be made according to clinical manifestations and the vitamin B12 dosage. Elevated serum homocysteine and elevated methylmalonic acid levels may be critical in diagnosing this deficiency. Elevated levels of methylmalonic acid are specific for diagnosis and its reduction occurs after treatment with vitamin B12<sup>1</sup>.

As for pain, the main symptom reported by the patient, and predominantly oral aphthae, at first caused great difficulty in diagnosis due to the non-specificity of the scenario. However, Behçet's disease was the main hypothesis, since it met the criteria described in table 2.

The diagnosis of Behçet's disease requires careful clinical observation, and there are no laboratory tests that can confirm it. It's a syndrome that can simulate several diseases, including vitamin B12 deficiency. Several diagnostic criteria have been proposed, including those recommended by the International Criteria for Behçet's Disease (ICBD), which was introduced in 2006 and revised in 2014 (Table 2)<sup>2</sup>. As noted in the table, the patient presented oral aphthae, genital aphthae, and folliculitis-like lesions, which although nonspecific were initially attributed to a possible Behçet's disease, since according to the ICBD, such a diagnosis should be considered if  $\geq 4$  points.

The pain condition, which had bothered the patient the most in recent months, was characterized by continuous pain in se-

veral body regions, without significant improvement with the use of analgesics or nonsteroidal anti-inflammatory drugs. Besides the diffuse pain, the appearance of a painful tongue lesion, with erythema and loss of papillae (Figure 1), suggested the diagnosis of hypovitaminosis B12, which was confirmed by low vitamin B12 dosages, increased homocysteine, and excellent response to vitamin B12 replacement. After 10 months of treatment, the patient presented resolution of the pain, disappearance of the oral and genital aphthae and the lesion on the tongue, as shown in figure 2. The patient remained asymptomatic during the entire follow-up period.

A review on the analgesic role of B-complex vitamins shows that they have analgesic effects in neuropathic and nociceptive pain syndromes, being safe and low-cost options for the treatment of some pain scenarios<sup>3</sup>.

Although the role of vitamin B12 in pain treatment is recognized by other authors, it has not been defined whether vitamin B12 deficiency could cause pain or not. There is no similar scenario in the literature of generalized and not well-defined CP with complete remission after replacement treatment with vitamin B12 administration. There are some reports of musculoskeletal pain starting after isotretinoin use, with improvement after introduction of vitamin B12<sup>4</sup>. One study<sup>5</sup> observed improvement in musculoskeletal pain symptoms in breast cancer patients undergoing treatment with aromatase inhibitors (anastrozole, letrozole, or exemestane) after treatment with vitamin B12.

Although critical evaluation and prospective randomized trials are needed, the reports add up to demonstrate the analgesic role of vitamin B12. On the other hand, it's important to note that for diseases that develop with significant pain, such as fibromyalgia, there are no studies demonstrating the relationship of pain with vitamin B12. One study<sup>6</sup> does not recommend dosing vitamin B12 routinely in patients with fibromyalgia. In the search for a biomarker for CP, another retrospective observational study<sup>7</sup> presented elevated levels of methylmalonic acid in 10% (n = 1.827) of patients, indicating vitamin B12 deficiency. In the same study, an alteration in homocysteine was found in 11% of patients, reinforcing the probable association with vitamin B12 deficiency.

Some authors point out the possibility of using vitamin B12 in the treatment of several etiologies of CP, including neuropathic<sup>8-10</sup>. However, such studies need further proof. Regarding the painful and repetitive oral aphthae that bothered the patient a lot, a study<sup>11</sup> mentions, among several causes, the importance of researching vitamin B12 deficiency.

Although several possible causes of vitamin B12 deficiency have been described<sup>12</sup>, it's likely that in the patient in this report the deficiency was due to inadequate diet, since other possibilities did not show conclusive results such as intestinal diseases compromising absorption, autoimmune diseases (negative Anti Parietal Cell AB and Intrinsic Anti-factor AB) or surgeries. The use of drugs that could cause the deficiency was not found. Vitamin B12 deficiency can occur even with apparently normal serum levels and absence of anemia, especially in early stages. It's important to include methylmalonic acid and homocysteine in the

**Table 2.** International classification criteria for Behçet disease (ICBD 2014)

Signs/symptoms	Score
Eye lesions	2
Genital aphthae	2
Oral aphthae	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test	1

investigation to increase the possibility of detecting the deficiency earlier, although these tests are not always available, especially methylmalonic acid.

## CONCLUSION

It's important to assess vitamin B12 deficiency in the differential diagnosis of chronic pain, and its association with the development of recurrent oral aphthae. Vitamin B12 replacement is effective, significantly improving the patients' quality of life.

## AUTHORS' CONTRIBUTIONS

### **Carolina Lamha Machado Carapinha**

Writing - Review and Editing

### **Heloína Lamha Machado Bonfante**

Writing - Preparation of the original, Writing - Review and Editing

### **Herval Lacerda Bonfante**

Data Collection, Writing - Preparation of the original, Writing - Review and Editing, Supervision

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