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CE - LETTER TO THE EDITOR

Chronic diarrhea: an unusual clinical presentation of vitamin B_{12} deficiency?

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Sir,

A 63-year-old male patient was admitted to our Internal Medicine Department with complaints of diarrhea lasting for more than 5 weeks (initially 12–15 evacuations/day of aqueous stool that progressed to 6–7 evacuations/day, with no blood or mucus). In addition, the patient mentioned nausea, almost daily vomiting and sporadic colicky abdominal pain. Fatigue and weight loss were also present. The subject denied occurrence of fever during the period in question.

He was a poorly controlled type 1 diabetic patient (HbA1C 8–8.5%), with peripheral neuropathy (diabetic foot), diabetic retinopathy and arterial peripheral disease (already submitted to multiple revascularization surgeries). The subject had arterial hypertension and dyslipidemia (both medicated) and had a previous hospitalization due to colonic ischemia (successfully addressed with conservative treatment). Moreover, he was taking omeprazole 20 mg daily to treat dyspeptic symptoms. No new drugs, lifestyle changes or recent traveling were reported. The patient reported no other medication or relevant clinical priors.

The physical evaluation on admission regarding vital signs, neurological and cardiopulmonary systems and abdominal examination was unremarkable, except for a thin appearance (IMC: 18.38 kg/m^2).

The hemogram revealed a normocytic normochromic anemia (Hb: 11.9 mg/dL, MCV: 97.3 fl, MCHC: 35.6 g/dL) that was not observed a year before and the electrolyte results showed hypokalemia (K+: 2.9 mEq/L, corrected during the first few days of hospitalization). The remaining analytical parameters addressing the kidney, hepatobiliary and thyroid function, as well as the iron levels and urinalysis, were normal. Leukocyte count and C reactive protein were also normal, and ferritin was elevated (445 ng/ml).

Collected stool samples (sent to physical, microbiological, virologic, parasitological and mycological analysis) had no relevant findings. Further analysis showed a fecal Na+ of 2 mEq/L and K+ of 12 mEq/L, with no fat detected.

During the diagnostic workup, a severe vitamin B_{12} deficiency (< 83 pg/ml) with normal levels of plasmatic folic acid (8.4 ng/ml) was detected. The patient denied being vegetarian. Upper and lower endoscopy and abdominal CT scan presented no relevant abnormalities. Antibodies against parietal cell, intrinsic factor and transglutaminase were negative. Supplementation with parenteral cyanocobalamin was implemented (1000 mcg once per day). A day after the first administration of vitamin B_{12}, the diarrhea stopped. The patient was re-evaluated 2 weeks after the hospital discharge, remaining free of gastrointestinal complaints and already reporting weight gain.

Our patient with chronic diarrhea had long term type 1 diabetes with multiple organ involvement. This fact led the medical team, at patient admission, to consider diarrhea due to autonomic neuropathy as a possible cause. However, as presented above, and after excluding the most common causes of chronic diarrhea, the clinical picture only improved after starting vitamin B_{12} supplementation. This vitamin is produced by bacteria and is usually obtained by consuming

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products of animal origin such as meat, fish, eggs or dairy products. After the ingestion and digestion of these types of food, vitamin B_{12} is linked with the intrinsic factor produced by the parietal cells of the stomach, being absorbed in the terminal ileus. It has an important role in DNA synthesis, methylation and mitochondrial metabolism, which makes this vitamin preponderant in rapidly growing cells (like those from gastrointestinal tract or bone marrow) and during the development, myelination and maintenance of the nervous cells. Thus, its deficiency causes several organic disturbances such as megaloblastic anemia, neuropathy, cognitive impairment and hearing loss, depression, and bone disease, among others [1].

If the origin of our patient's diarrhea were the above-mentioned autonomic neuropathy, the liquid feces would have persisted even after the replenishment with cyanocobalamin, which strengthens the idea that this deficiency may have an etiologic role in this clinical presentation. This may happen due to a cytopathic effect of low vitamin B_{12} levels on the enterocyte's metabolism and division, which can favor the diarrhea occurrence. Although rare, this idea is not new: *Mirijello* and colleagues described in 2015 a similar case of a 65-year-old diabetic woman with severe cyanocobalamin deficiency that also resolved her chronic diarrhea after starting supplementation [2].

One of the most frequent causes of vitamin B_{12} deficiency in diabetic patients is related to metformin usage [3] (as probably happened in the clinical case of *Mirijello* and colleagues); however, our patient was not taking this medication. One possible explanation could be small intestinal bacterial overgrowth (SIBO), a medical condition in which the small bowel is colonized by excessive aerobic and anaerobic bacteria that are usually present in the colon. This pathology can be the result of motility disorders (amyloidosis, diabetic neuropathy, …), gastric hypocloridia (proton pump inhibitors, …), immune, anatomic and metabolic disorders, leading to vitamin B_{12} consumption by the bacteria. It can present with bloating, flatulence, abdominal discomfort, or chronic watery diarrhea. A positive carbohydrate breath test or a bacterial concentration of $> 10^3$ colony forming units/mL in a jejunal aspirate culture could establish the diagnosis [4] but, unfortunately, they were not performed in this clinical case. Despite this fact, the diarrhea resolved only with cyanocobalamin and without the institution of any antibiotic regimen, what is, at least, unexpected if SIBO was the cause.

Another putative explanation to our case could be the proton pump inhibitor (PPI) omeprazole. Absorption of cyanocobalamin involves peptic enzymes to cleave dietary vitamin B_{12} from the proteins of the diet. This process is performed mainly by pepsin, which requires the low pH resulting from the gastric acid to be activated from its pepsinogen precursor. Without this acidic medium, this vitamin would not be cleaved from dietary proteins and would not be able to bind other proteins that protect cyanocobalamin from the digestion promoted by pancreatic enzymes, which leads ultimately to decreased vitamin B_{12}absorption. Therefore, it has been hypothesized that conditions related with impaired acidic production (such as pump inhibitors consumption) may lead to malabsorption and cyanocobalamin deficiency. Although there are some studies suggesting an increased risk of vitamin B_{12} deficiency in patients taking PPI, prospective trials are needed to prove a direct cause-and-effect relationship between PPI and cyanocobalamin deficiency [5].

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Hunt A, Harrington D, Robinson S (2014) Vitamin B12 deficiency. BMJ 349:5226–g5226
2. Mirijello A et al (2016) Chronic diarrhea in a patient with severe vitamin B12 deficiency: a rare clinical manifestation.". Scand J Gastroenterol. 51(6):763–764
3. Chapman LE, Darling AL, Brown JE (2016) Association between metformin and vitamin B_{12} deficiency in patients with type 2 diabetes: a systematic review and meta-analysis. Diab Metabol 42(5):316–327
4. Grace E et al (2013) Review article: small intestinal bacterial overgrowth–prevalence, clinical features, current and developing diagnostic tests, and treatment. Aliment Pharmacol Ther. 38(7):674–688
5. Heidelbaugh JJ (2013) Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf. 4(3):125–133