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Case Report

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Nutritional Bicytopenia in the Context of a Very Low-Calorie Diet with Adequate Micronutrient Supplementation

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ABSTRACT

The aim of this study is to establish the ideal clinician's approach to nutritional bicytopenia in the context of adequate micronutrient supplementation. We present the case of a 27-year-old patient living with obesity, subjected for months to a very low-calorie diet and adequate supplementation with complementary vitamins and minerals, evaluated and treated for bicytopenia with iron-deficiency anemia and lymphocytopenia. The use of meal replacement supplements as nutritional sources replacing food items requires medical supervision as they can have consequences on the patient's micronutrient balance. Classically, and frequently, iron-deficiency anemias have been identified as the most common condition in these restrictive nutritional regimens. However, alterations in the white cell line are more frequent than believed and may be associated with multiple nutritional deficiencies including folic acid and vitamin B12. The diagnostic approach becomes complex when the most common nutritional causes are hidden by replacement supplements. The patient achieved an increase in hemoglobin after treatment (12.3 g/dL), recovering from anemia. When approaching nutritional cytopenias, the primary takeaway should always be the thinking process. Every patient with bicytopenia must be studied particularly meticulously, and the good clinician is forced to address it and reach the most likely diagnosis within the common and the rare.

Keywords: Anemia, folic acid, iron-deficiency anemia, leukopenia, lymphopenia, vitamin B12

INTRODUCTION

Iron, vitamin B12, and folic acid are the basic nutrients the bone marrow uses to build hematopoietic cells. When any of the above are no longer supplemented correctly, nutritional anemias can occur due to direct impairment in the synthesis and maturation of hematopoietic cells.[1] These cells begin to be reduced in quantity and size, having a clinical impact on the patient and causing specific symptoms to the affected cell line. Anemias are classified as microcytic when the mean corpuscular volume (MCV) is less than 80 fl.[2] Iron deficiency is by far the major cause of microcytic anemia, but pyridoxine and copper can cause it as well. Normocytic anemias are common in patients with protein-energy malnutrition and various chronic diseases, and macrocytic anemias can be caused by vitamin B12 or folic acid deficiencies.[3] The coexistence of iron and folic acid deficiencies is common and can be confirmed with a blood smear examination, measuring the suspected deficient nutrient blood level, or a bone marrow study. Therapeutic response to deficient nutrient replacement is the hallmark to define nutritional anemia.[4]

The etiology of anemia can be divided into 3: (i) hemolysis, (ii) blood loss, and (iii) diminished erythropoiesis. Once the first 2 options are evaluated and discarded, erythropoiesis must be studied by the first diagnostic test available in most laboratories: a complete blood count and smear. Iron deficiency occurs when serum ferritin is <30 ng/mL, transferrin saturation is <19%, the anemia resolves with iron replacement, or absence of stainable iron in the bone marrow.[5]

On the other hand, leukopenia associated with iron-deficiency anemia in the context of a very low-calorie diet, with adequate supplementation of folic acid, vitamin B12, copper, and zinc, should be evaluated as a nutritional consequence of iron deprivation.[6]

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CASE PRESENTATION

A 27-year-old female, previously healthy, with a body mass index of 30 g/m^2 and with no medical or pharmacological history, reports having undergone a very low-calorie diet (<800 kcal/day) for 6 months and supposedly adequate supplementation of vitamins and minerals.

She sought a second opinion for the symptoms she was experiencing for about 3 months and was managed in an outpatient clinic. Upon being questioned, she indicated she was experiencing dizziness, fatigue, pale integuments, and palpitation. She denied having a regular menstrual cycle. Physical examination showed pale mucous membranes and integuments, tachycardia, and postural weakness. No hepato-splenomegaly.

Initial hemoglobin (Hgb) 8.2 g/dL (normal value 12-15 g/dL), MCV 60 fL (normal value 80-95 fl), with hypochromia, leukocyte count of 3.5 × 10^9/µL (normal value 4.5-11.0 × 10^9/L), and normal platelets (normal value 150-400 × 10^3/µL). Additional lab tests were required on the same day. Complete results were red blood cell (RBC) count 5.0 × 10^6/µL (normal range 3.8-4.8 × 10^6/µL), Hgb 8.2 g/dL (normal range 12.0-15.0 g/dL), ferritin 12.5 ng/mL (normal range 15-204 ng/mL), transferrin saturation 5% (normal range 20%-50%), Iron 15 µg/dL (normal range 50-170 µg/dL), leukocytes 3.5×10^9/µL (normal range 4.5-11.0 ×10^9/L), platelets 322×10^3/µL (normal range 150-400×10^3/µL), vitamin B12 320 mIU/L (normal range 145.0-596.0), folic acid 15.1 nmol/L (normal range 2.70-16.30 nmol/L), thyroid-stimulating hormone 11.2 mIU/L (normal range 0.700-3.400 mIU/L), free thyroxine 4 fraction 10.7 mIU/L (normal range 7.9-13.9 mIU/L). One week and 2 weeks later, Hgb tests were made with 10.1 g/dL and 12.3 g/dL results, respectively.

This patient was treated in an outpatient clinic, and follow-up visits were held in the same place.

Main Points

- The use of supplementation in restrictive nutritional regimens requires meticulous medical supervision.
- Iron-deficiency anemia remains the most common deficiency in these nutritional regimens.
- When more than 1 blood cell line is affected, folic acid and B12 deficiencies should be addressed.
- In patients with bicytopenia and proper nutritional supplementation, autoimmune, infectious, and hormonal causes must first be ruled out.
- Patients with bicytopenia must be studied meticulously and addressed by the most likely etiology and the rare.

RESULTS

An iron deficiency of approximately 1.5 g was calculated. Due to intolerance of oral iron, this deficiency was managed with ferric carboxymaltose in 2 infusion sessions in an outpatient clinic. Additionally, the patient was orally supplemented with micronutrient complements, such as vitamin B12 and folic acid in the daily recommended dosage.

The patient achieved an increase in hemoglobin of 12.3 g/dL after a 2-week treatment, recovering from anemia (Table 1).

DISCUSSION

Bicytopenia can be a life-threatening condition if a proper diagnosis, treatment, and follow-up are not defined correctly. Although there may be transient cytopenias due to infections in the etiology, serious diseases related to the bone marrow can also be seen. Etiology ranges from inflammatory diseases, infections, transient suppression of the bone marrow, and of course, nutritional deficiencies.[7] According to the etiologic cause, cytopenias can be explained by maturation defects, ineffective hematopoiesis, infiltration of the bone marrow, and cell destruction.

Table 1. Laboratory Results

Laboratory Parameter	Value	Normal Range
RBC	5.0 × 10^6/µL	3.8-4.8 × 10^6/µL
Hgb	8.2 g/dL	12.0-15.0 g/dL
Ferritin	12.5 ng/mL	15-204 ng/mL
Transferrin saturation	5%	20%-50%
Iron	15 µg/dL	50-170 µg/dL
Leukocytes	3.5 × 10^9/µL	4.5-11.0 × 10^9/L
Platelets	322 × 10^3/µL	150-400 × 10^3/µL
Vit. B12	320 mIU/L	145.0-596.0 mIU/L
Folic acid	15.1 nmol/L	2.70-16.30 nmol/L
TSH	11.2 mIU/L	0.700-3.400 mIU/L
fT4	10.7 mIU/L	7.9-13.6 mIU/L
Hgb*	10.1 g/dL	12.0-15.0 g/dL
Hgb**	12.3 g/dL	12.0-15.0 g/dL

fT4, free thyroxine 4 fraction; Hgb, hemoglobin; TSH, thyroid-stimulating hormone; Vit. B12, vitamin B12.
*Before treatment.
**After treatment.

Iron deficiency is the most common cytopenia reported in malnutrition, and its approach to evaluation, diagnosis, and treatment is relatively simple when the suspicion of malnutrition is detected in the medical history.[8] In the face of significant malnutrition due to dietary restrictions, cell lines are theoretically affected by folic acid and vitamin B12 deficiency, and not only from iron.[9,10] The last thing to consider is the approach to leukopenia when we know in advance that the patient had adequate replacement of folic acid and vitamin B12 for at least 6 months when she underwent the caloric regime and that is when we have to think about studying the white cell line alone or collectively as bicytopenia.[11] Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) without any other manifestation in the physical exam would be extremely rare. Cancer and bone marrow failure should be considered and analyzed with a bone marrow aspirate and biopsy if no response to basic treatment is shown. The influence of medications is ruled out in medical history. Infections, especially those of viral etiology, can cause leukopenia to have at least some type of symptoms, which was not the case. Hypothyroidism can be ruled out with an initial thyroid exam.[12-15]

Clinical thinking of the internist always has to fully evaluate the patient, and define what is really probable, based on the most common causes, medical history, and physical examination. The association between iron-deficiency anemia and leukopenia has been related in the past, denoting bone marrow failure due to the deficiency itself.[16] However, the separate diagnostic approach to leukopenia does not confer a unique study purpose. It is here when the therapeutic test with iron has relevance, since when prescribed, bicytopenia can remit.

Nicotinamide adenine dinucleotide phosphate hydrogen-dependent oxidative burst, as well as other monocyte/macrophage differentiation processes, requires iron as a cofactor.[17] In vitro production of cytokines by lymphocytes studies have shown impairment to iron deficiency in the past.[5,18,19]

If the patient had not been adequately supplemented with vitamins and minerals, bicytopenia should no longer be considered clearly associated with nutritional deficiency due to inadequate intake. However, having 2 altered cell lines, which can be explained by different mechanisms, forces the clinician to go further in the diagnosis of leukopenia, and at least rule out the improbable and the most common within the logic and context of the patient.
When approaching nutritional cytopenias, the primary takeaway should always be the thinking process. First of all, the evaluation of possible nutritional deficiencies is primary cause of this condition. In certain cases in which there is evidence that the patient has been adequately supplemented nutritionally with the elements necessary to produce RBCs, white blood cells, and platelets, autoimmune, infectious, and hormonal causes must first be ruled out. If all of the above are within normality, the less frequent cases should be considered, such as bicytopenia, secondary to vitamin or mineral deficiency.

In this new era, in which restrictive diets with adequate vitamin and mineral supplementation are in vogue, every patient with bicytopenia must be studied meticulously, and a good clinician is forced to address it and reach the most likely diagnosis within the common and the rare.

Informed Consent: Informed consent has been obtained from the patient to process the information in the case report.

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