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Hypocupremia-related anemia and neutropenia late after Roux-en-Y gastric bypass surgery

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Abstract

Roux-en Y gastric bypass (RYGB) is a type of surgery that is both restrictive in food intake and malabsorptive. The prevalence of copper deficiency (hypocupremia) has been reported as 10%-%20 after RYGB. Copper deficiency has started to appear more frequently due to bariatric surgical procedures, which are widely applied all over the world and in our country, but it is often not recognized. In order to raise awareness on the subject, we wanted to present a patient who developed copper deficiency and secondary anemia and neutropenia after RYGB.

Introduction

The most effective and permanent method in the treatment of obesity is bariatric surgery, but the occurrence of malnutrition and nutrient deficiencies after most bariatric procedures requires close postoperative follow-up of the patients. Roux-en Y gastric bypass (RYGB) is a type of surgery that is both restrictive in food intake and malabsorptive [1]. Vitamin D, vitamin B family, calcium, iron, and zinc deficiencies can be counted as the most common vitamin and mineral deficiencies. Another deficiency that is more difficult to recognize is copper deficiency. The prevalence of copper deficiency (hypocupremia) has been reported as 10%-%20 after RYGB [2]. Deficiency often affects the hematological and neurological systems. Hematological findings return within 6-12 weeks with copper replacement, but neurological findings are often permanent [3]. Although replacement stops progress, it does not improve the current situation. Copper deficiency has started to appear more frequently due to bariatric surgical procedures, which are widely applied all over the world and in our country, but it is often not recognized. In order to raise awareness on the subject, we wanted to present a patient who developed copper deficiency and secondary anemia and neutropenia after RYGB.

Case Report

A 49-year-old female patient presented with complaints of weakness, fatigue, dizziness, drowsiness, shortness of breath and palpitations. She had no known chronic disease. RYGB operation was performed 8 years ago due to morbid obesity. She went through menopause 2 years ago. Since the COVID 19 pandemic, she was using daily 50 mg of zinc sulfate and 1200 I.U. vitamin D3 regularly for about 3 years. In addition, she was using B12, iron, folic acid, and calcium intermittently without blood analysis after bariatric surgery. She stated that he last used these vitamins 5-6 months ago. On physical examination, he appeared pale, blood pressure was 95/55 mmHg, and heart rate was 108. Heart and lung sounds were normal and abdominal examination was unremarkable. In blood tests, fasting blood glucose, lipid profile, liver, kidney and thyroid functions were within normal limits. Sedimentation and CRP were negative. In complete blood count pathologically, hemoglobin 9.3 g/dl, MCV:71 fL, iron: 15 µg/dL, ferritin: 4.4 ng/Ml, neutrophil 0,48 10^3/uL was detected. Platelet count was normal. Stool occult blood was negative. B12, folic acid, calcium and vitamin D levels were

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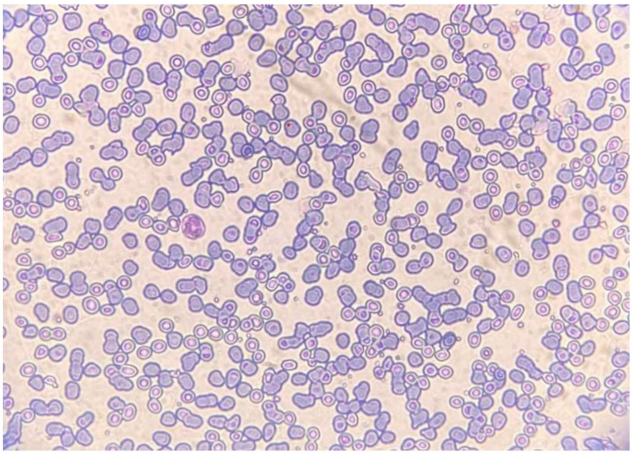

Figure 1. Peripheral smear findings -hypochromic microcytic erythrocytes, anisocytosis, poikilocytosis, target cells.

normal. Zinc was slightly elevated. Copper was detected at 47 ug/dL (N: 80-155). When the peripheral smear was examined, hypochromic microcytic erythrocytes, anisocytosis poikilocytosisa and target cells were observed (Figure 1). Copper sulfate 4 mg/day + 80 mg/day ferrous sulfate was prescribed. Zinc use was stopped. At the end of 8 weeks, it was observed that his complaints completely regressed and Hgb, MCV, iron / ferritin, neutrophil, copper values increased to normal limits. All blood values of the patient before and after treatment are given in Table 1. The patient was informed about the case presentation and the consent form was signed by her on 16.03.2023.

Table 1. Laboratory parameters before and after treatment.

Laboratoy Parameter	May, 2023	July, 2023
Hemoglobin g/dl (N: 11.6-15.5)	9.3	12.1
Mean Cell Volume (MCV) Fl (N: 80-98)	71	82
Iron (Fe) µg/Dl (N: 33-193)	15	67
Ferritin ng/Ml (N: 13-150)	4.4	20.6
Neutrophil 10^3/Ul (N: 1.5-7.1)	0.48	2.3
Vitamin B12 pg/mL(N: 197-771)	328	
Folate ng/Ml (N: 2.2-20.6)	6.9	
Calcium mg/Dl (8.5-10.2)	8.6	
Vitamin D ng/mL(N: 30-80)	51.2	
Copper (Cu) ug/dl (N: 80-155)	47	89
Zinc (Zn) ug/dL(N: 60-120)	127	

Discussion

Copper is an element that is absorbed from the stomach, duodenum and jejunum. Copper is a cofactor of biologically important oxidative enzymes such as cytochrome c oxidase and superoxide dismutase. It is necessary for cellular respiration, bone marrow functions, vascular development, and removal of free radicals, central nervous system functions and protection of skeletal health [4]. European Food Safety Authority guidelines recommend a daily copper intake of 1.6 mg for men and 1.3 mg for women [5].

Sleeve gastrectomy, RYGB and biliopancreatic diversion - Duodenal switch are the main procedures associated with nutrient deficiencies due to changing anatomy and physiology [6]. The status of micronutrients should be monitored both before and after surgery at certain periods. Calcium, vitamin D, iron, zinc, vitamin B family deficiencies may develop. These vitamins and minerals are well known and followed by clinicians. They should be followed every 3-6 months in the first year and every 6-12 months in the following years [7]. Copper, on the other hand, is an element that we want less in our routine and can be skipped in pursuit. Copper deficiency develops in 1-2 out of every 10 patients in the long term after RYGB. Although there are other conditions that cause its deficiency, the biggest reason is surgery. In a study in which 40 patients with copper deficiency were evaluated retrospectively, it was shown that 25% of the patients had bariatric surgery and 35% had gastrointestinal system surgery [8].

Another point that causes copper deficiency and which clinicians should be careful about is that excessive intake of zinc causes copper deficiency. Copper is taken up into cells via the copper transporter 1 (CTR1) located in the apical cells of the gastrointestinal tract epithelium. When copper enters the cell, it combines with a protein called metallothionain. This protein ensures that copper is stored in the cell. Metallothionaine has greater affinity for copper than for zinc. Zinc increases the amount of this protein, so copper remains bound to the protein, and zinc enters the systemic circulation from intestinal epithelial cells [9]. In our case, our patient had been using zinc to keep the immune system strong for about 3 years after the COVID 19 pandemic. We think that this contributes to the development of the deficiency. A minimum of 2 mg copper intake per day is recommended to prevent deficiency after RYGB. The most important consequences of copper deficiency are related to the hematological and neurological systems. It often presents with anemia, neutopenia, less commonly thrombocytopenia and pancytopenia. Anemia can be microcytic, normocytic, or macrocytic. The main reason why copper deficiency causes anemia is the failure of the enzymes responsible for oxidation. When the mitochondria of the animals with copper deficiency were examined, it was observed that the cytochrome activity was insufficient, heme synthesis could not be performed in sufficient amounts by using protoporphyrin and ferric iron, and iron accumulated in the mitochondria [10]. In addition, hephaestin and ceruloplasmin, which are copper-dependent proteins and whose task is to transport iron, cannot function adequately. Hephaestin ensures the absorption of iron from intestinal cells, while ceruloplasmin ensures that tissue iron enters the circulation [11].

In our case, although our patient had no signs of bleeding and was using iron intermittently, she had iron deficiency as well as copper deficiency, and hypochromic microcytic erythrocytes and anisocytosis were observed in her peripheral smear, consistent with this.

Our patient also had neutropenia. In the development of neutropenia suggested etiologies have included destruction of myeloid progenitor cells the bone marrow, inhibition of

differentiation and self-renewal of CD34+ hematopoietic progenitor cells, impaired egress of neutrophils from the bone marrow, and increased clearance of neutrophils from the circulation [12].

There was no neurological involvement in our case, but we can count the neurological findings as gait disturbances, ataxia, and spasticity. Subcortical white matter changes, cerebellum atrophy, dorsal column signal changes can be detected by magnetic resonance. These deficits are similar to B12 deficiency. Copper supplementation prevents the progression of the current condition, but may not improve [13]. Another point to be considered when looking at the serum copper level is whether there is a condition with inflammation. Because the serum copper transporter ceruloplasmin is an acute phase reactant, it may be high in case of inflammation, which may cause a low copper level to appear high. In our case, CRP and sedimentation values were within normal limits.

A treatment is planned according to how much copper is deficient in the treatment and the condition of the symptoms. There are 3 forms that can be replaced: copper sulfate, copper gluconate and copper chloride. As in our case, 3-8 mg copper gluconate / sulfate replacement is recommended until blood values return to normal in mild to moderate deficiencies. In severe deficiency, intravenous replacement of 2-4 mg of copper chloride daily can be planned for a maximum of 6 days until the serum copper level returns to normal. Since IV copper replacement can cause serious complications such as hemolysis and liver necrosis, it should not be performed unless necessary. After serum copper levels return to normal, they should be monitored every 3 months [14].

Hematological findings are expected to be completely resolved in 12 weeks at the latest. In our case, a complete clinical and laboratory response to the combined replacement of copper and iron was obtained in 8 weeks.

Conclusion

Copper deficiency is a condition that is becoming more common due to bariatric surgery procedures, which are becoming increasingly common all over the world and in our country. When it is recognized and treated, full clinical recovery can be achieved, but when it is not noticed, it may have irreversible consequences. For this reason, it is very important to follow copper like other vitamins and minerals in patients who have undergone gastrointestinal system surgery, and also to be well aware of the clinical and laboratory findings that may occur.

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