Correction of Copper Deficiency Improves Erythropoietin Unresponsiveness in Hemodialysis Patients with Anemia

Terumi Higuchi¹, Yoshihiro Matsukawa², Kazuyoshi Okada¹, Osamu Oikawa¹, Toshio Yamazaki¹, Yoshihiko Ohnishí¹, Takayuki Fujita¹, Noboru Fukuda¹, Masayoshi Soma¹ and Koichi Matsumoto¹

Abstract

We have encountered five hemodialysis patients who had received enteral nutrition and recovered from erythropoietin-resistant anemia with neutropenia after the correction of copper deficiency. We reduced the required doses of recombinant human erythropoietin (rHuEPO) to maintain the target hematocrit levels and three patients were finally weaned from the rHuEPO therapy. Thus, copper deficiency is involved in erythropoietin-resistant anemia in hemodialysis patients.

Key words: copper deficiency, anemia, enteral nutrition, erythropoietin

(DOI: 10.2169/internalmedicine.45.1541)

Introduction

Recombinant human erythropoietin (rHuEPO) has been recognized as being effective in the treatment of anemia associated with chronic renal failure (CRF) (1). While, erythropoietin-resistant anemia has been reported in hemodialysis patients (2). Causes of the erythropoietin-resistant anemia in hemodialysis patients have been reported to be associated with iron deficiency (3), secondary hyperparathyroidism (4), chronic inflammatory state (5), accumulation of aluminium (6), and vitamin deficiency (7) and so on. Copper is known as an essential trace element and is a component of copper metalloenzymes. Among the many manifestations observed in acquired copper deficiency, this condition causes anemia with neutropenia (8). We have encountered five hemodialysis patients who recovered well from rHuEPO-resistant anemia after correction of copper.

Case Report

A 61-year-old representative hemodialysis woman developed cerebral infarction and suffered from the after-effects of bulbar palsy and tetraplegia. We thus initiated enteral nutrition. Six months later, anemia and neutropenia developed: RBC 130×10⁴/μl, hemoglobin 4.7 g/dl, hematocrit 14.7%, MCV 118fl, MCHC 32.0% and WBC 1500/μl. The type of anemia was macrocytic, however, pernicious anemia was negligible: vitamin B12 and folic acid were normal. The pathogenesis of this anemia with neutropenia was undetermined, and we conducted blood transfusion and granulocyte colony stimulating factor. Subsequently, we noticed that the dose (120 μg/day) of copper in the enteral nutrition was insufficient and verified the serum levels of both copper and ceruloplasmin as being low (8: normal 78 to 131 μg/dl, and 3.6: normal 21 to 33 mg/dl, respectively). Copper supplementation of 2 mg/day (copper sulfate) was initiated. Four weeks later, the following improvements were confirmed: RBC 271×10⁴/μl, hemoglobin 9.0 g/dl, hematocrit 28.3%, WBC 5,600 /μl, copper 84 μg/dl and ceruloplasmin 28.4 mg/dl. Subsequently, we successfully decreased the maintenance dose of rHuEPO to 500 IU/week, resulting in reduction of the previously required dose (9,000 IU/week) (Fig. 1).

Four other hemodialysis patients with rHuEPO-resistant anemia were also improved with copper correction (Ta-
They also were hospitalized due to cerebral infarction or hypoxic encephalopathy and received enteral nutrition. Their rHuEPO-resistant anemia with neutropenia developed from 8 to 12 months after receiving enteral nutrition with an insufficient content of copper. We changed to other artificial enteral nutrition formula (ENSURE LIQUID®: Abbott Laboratory, Chicago, USA) containing a higher dose of copper (1.2 mg/day). Three months of such treatment improved the following parameters: copper 7-10 to 88-101 μg/dl, ceruloplasmin 2.0-3.2 to 24.8-26.6 mg/dl, RBC 130-224 to 324-358×10⁴/μl, hemoglobin 5.5-7.4 to 10.1-11.3 g/dl, and WBC 1,400-2,100 to 5,000-9,000 /μl. In all cases, macrocytic changes in RBC and neutropenia were normalized with copper supplementation and the required doses of rHuEPO could be reduced. Three patients became free from rHuEPO. However, it was necessary to administer...
calcium polystyrene sulfonate for hyperkalemia because of the excessive dose of potassium contained in the enteral nutrition formula.

**Discussion**

Copper deficiency is a rare condition, but with unusual types of nutrition, such as enteral nutrition and total parenteral nutrition, anemia and neutropenia due to copper deficiency may occur.

The mechanism by which copper deficiency induces anemia, erythropoietin-resistant anemia and other cytopenias is unclear. Copper is an essential co-factor for various redox enzymes (9), and the low activity of copper-dependent enzymes such as ceruloplasmin ferroxidase and cytochrome oxidase, has been hypothesized to be a potential cause of anemia (10). Mitochondria isolated from copper-deficient animals were lacking in cytochrome oxidase activity and failed to synthesize heme from ferric iron and protoporphyrin at the normal rate, perhaps leading to mitochondrial iron accumulation (11). In addition, copper/zinc superoxide dismutase (Cu/Zn-SOD), an antioxidant enzyme, activity is decreased to 20% of the normal erythrocyte Cu/Zn-SOD in the copper-deficient subject, which may accelerate disposision of superoxide and shorten the life span of erythrocytes (12).

Previous studies have reported that copper deficiency anemia by adequate copper supplementation gradually improved after three months and neutrophil counts also returned to normal within 2–4 weeks (13, 14). The dose of copper administered to the present five patients was 117 mg during the three-month period.

Hemodialysis patients suffer from several complications including stroke. Stroke patients sometimes receive total parenteral nutrition or enteral nutrition induced by a variety of complications, which may subsequently cause copper deficiency. To prevent copper-deficient anemia, artificial nutrition preparations containing adequate doses of copper should be used. At present, nutrition preparations containing adequate calorie, electrolytes, trace elements and substances for CRF patients are unavailable in Japan. We await the development of suitable artificial nutrition preparations for CRF patients.

To date, there have been no reports on anemia due to copper deficiency in hemodialysis patients. We first reported that correction of the copper level improved rHuEPO-resistant anemia in hemodialysis patients. Excessive administration of rHuEPO for the treatment of anemia in hemodialysis patients raises economical burdens, which can be reduced by an adequate supplement of copper. Thus, clinicians should pay careful attention to the anemia observed in hemodialysis patients with special reference to the macrocytic changes in RBC and neutropenia to rule out copper deficiency anemia and to prevent excessive administration of erythropoietin. In conclusion, copper deficiency is a novel mechanism in erythropoietin-resistant anemia in patients with CRF.

**References**