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Case Report

Pancytopenia after Removal of Copper from Total Parenteral Nutrition

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ABSTRACT. Patients who develop cholestatic jaundice during chronic total parenteral nutrition (TPN) can develop significant hematologic complications due to hypocupremia if copper supplementation is withheld. A 36-year-old female with short bowel syndrome developed progressive liver dysfunction 6 months after initiation of TPN. Trace elements were omitted from her TPN because of cholestasis and persistent hyperbilirubinemia. Despite chronic diarrhea, absorption of some dietary copper was anticipated from her oral diet. Fifteen months later, the patient became red cell transfusion dependent, and her neutrophil and platelet counts steadily declined. After 19 months of receiving TPN without trace elements, her serum copper level was 25 μg/dL (normal: 70 to 155 μg/dL). Provision of trace elements for 2 months was associated with increased serum copper, neutrophil and platelet counts and independence from red cell transfusions. When the serum copper level reached 186 μg/dL, copper supplementation was discontinued. Over the next 3 months, serum copper level fell to 10 μg/dL, neutrophil and platelet counts fell precipitously, and red cell transfusions were resumed. Once again, copper, neutrophil and platelet levels promptly rebounded with parenteral copper supplementation. Although anemia and neutropenia are well-recognized hematologic consequences of copper deficiency, thrombocytopenia rarely has been reported. This is the first report of pancytopenia secondary to TPN-related copper deficiency in which the association was confirmed when hypocupremia recurred. (*Journal of Parenteral and Enteral Nutrition* **24**:361–366, 2000)

Copper is routinely added to parenteral nutrition solutions as a component of a trace element preparation after reports of hematologic (anemia and neutropenia) complications in adults and hematologic, skeletal, and neurologic complications in children due to total parenteral nutrition (TPN)- associated copper deficiency.[1] However, because copper is excreted primarily in the bile, some experts advocate reducing or curtailing copper supplementation in patients who develop chronic hyperbilirubinemia during chronic TPN.[2–4] This is a case report of a patient with short bowel syndrome and TPN-associated hyperbilirubinemia complicated by hypocupremia and pancytopenia as a result of omission of copper from the parenteral nutrition solution.

CASE REPORT

In January 1994, a 39-year-old woman presented with acute abdominal pain and peritonitis and required an emergency exploratory laparotomy. Extensive small bowel infarction secondary to a thrombosed superior mesenteric vein necessitated a subtotal small bowel resection with primary anastomosis of 30 cm of proximal duodenum to 30 cm of distal ileum. Colonic continuity was maintained. Subsequently, she experienced chronic malabsorption due to short bowel syndrome and required chronic TPN. Evaluation for congenital and acquired risk factors for venous thromboembolisms was notable for homozygosity for Factor V Leiden and concurrent use of oral contraceptive pills.

The patient developed elevated aspartate aminotransferase (AST, 93 U/L; normal, 12 to 50 U/L), alanine aminotransferase (ALT, 83 U/L; normal, 3 to 55 U/L), and γ-glutamyltransferase (GGT, 139 U/L; normal 10 to 60 U/L) in July, 1994. A liver biopsy showed mild portal inflammation, and serologies for Hepatitis A, B, and C were negative. Her TPN was adjusted to provide estimated energy needs (BEE × 1.3), with a mixed fuel of lipids, amino acids, dextrose, and Vitamin B_{12} (5 mg/d). However, 8 months later, a rise in serum bilirubin to 10.9 mg/dL (normal, 0.2 to 1.3 mg/dL) prompted a second liver biopsy, which demonstrated mild steatosis, early fibrosis, and cholestasis consistent with metabolic complications from chronic TPN. Endoscopic retrograde cholangiopancreas (ERCP) examination demonstrated no biliary obstruction or strictures. Because of concerns that IV copper administration could cause hepatic copper overload in the setting of cholestatic jaundice and the expectation that some dietary copper would be absorbed through her remaining small bowel, daily trace element supple-

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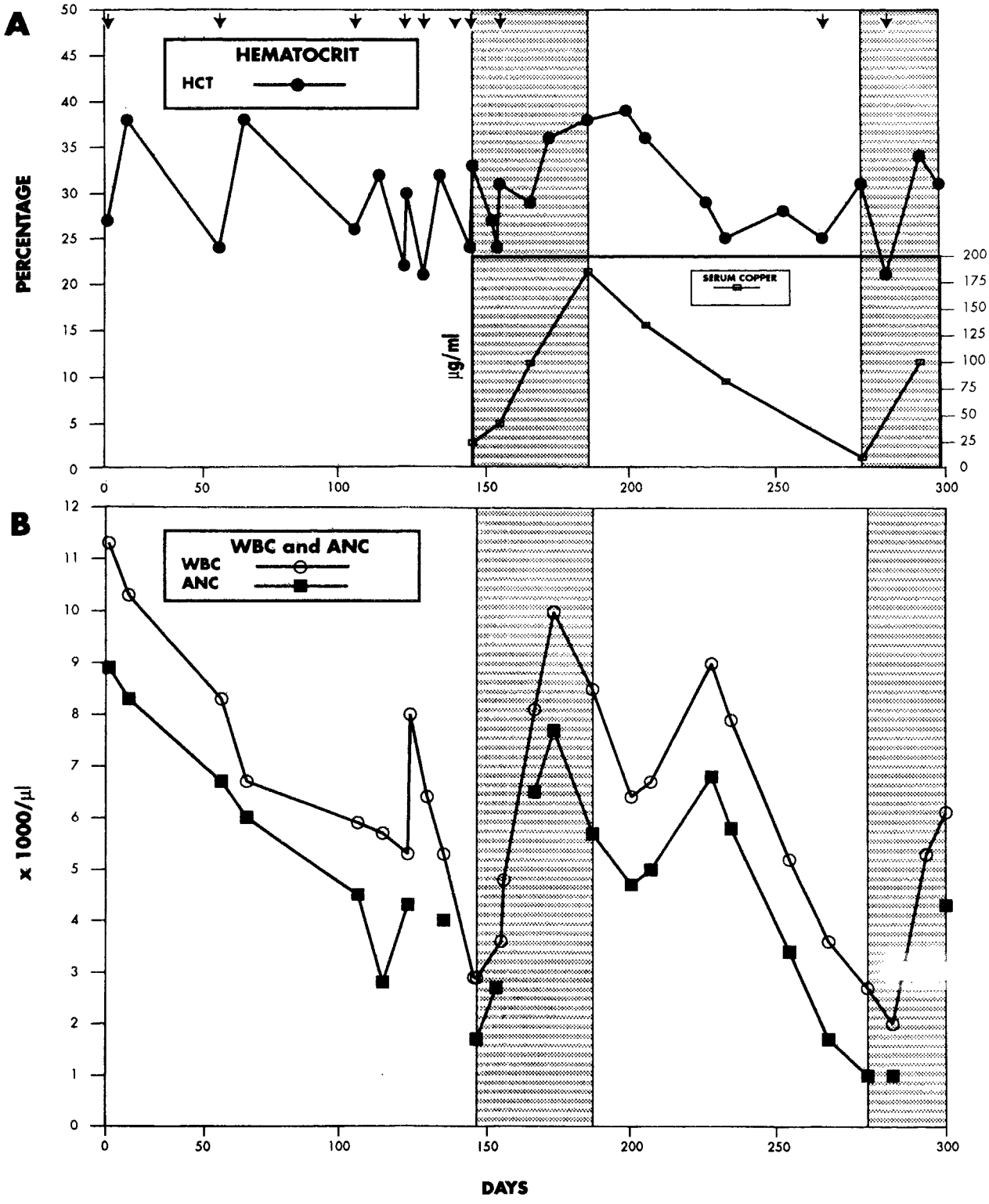

FIG. 1. Effect of copper deficiency and supplementation on patient's hematologic values after first red cell transfusion (day 1). (*A*) Hematocrit (normal range, 39% to 50%); ↓, transfusion of two units of red cells; inset, serum copper levels (normal range, 70 to 155 µg/dL). (*B*) WBC, white cell count (normal range, 3.5 to 10.5 × 10^3/µL); ANC, absolute neutrophil count (normal range, 1.7–7.0 × 10^3/µL); breaks in ANC graph indicate days WBC differential was not ordered. (*C*) Platelet count (normal range, 150 to 400 × 10^3/µL). Shaded vertical bars indicate periods when 1 mg elemental copper was added to daily TPN.

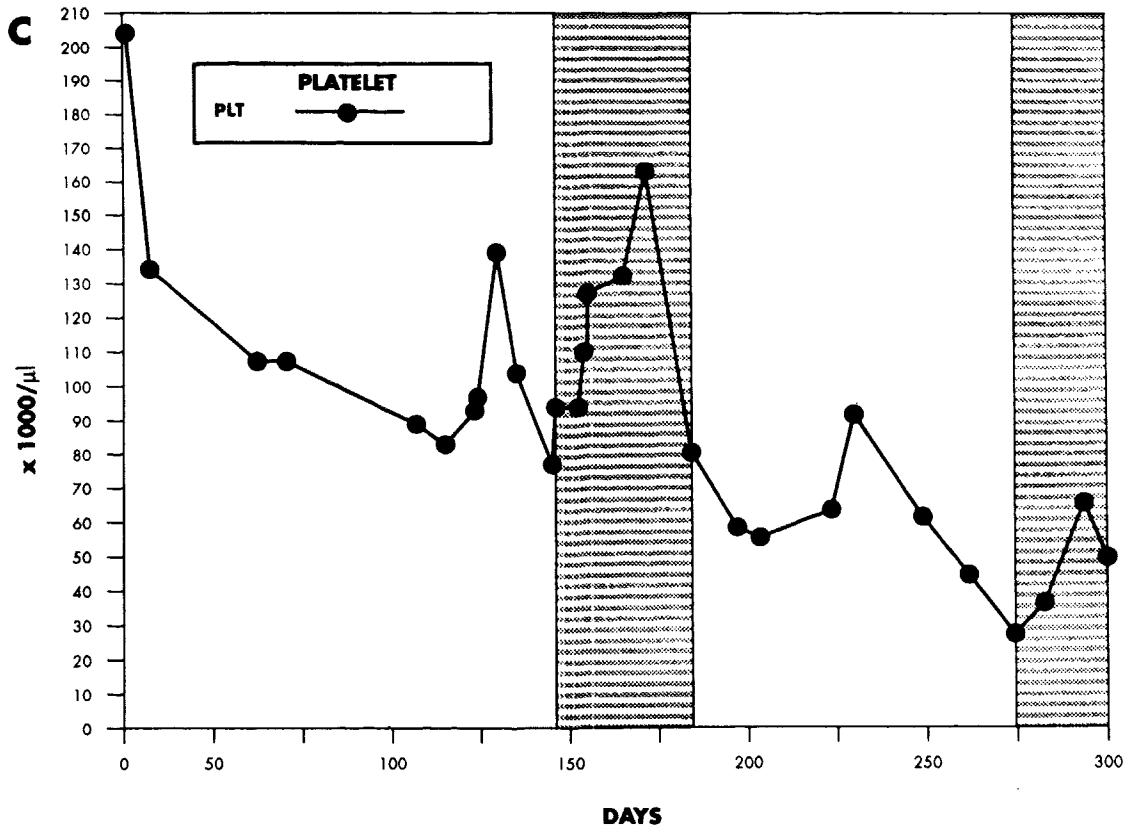

FIG. 1. *Continued*

ments (copper 1 mg, chromium 10 μg, manganese 0.5 mg), except for zinc (5 mg), were deleted from the TPN.

During the next 12 months unsuccessful attempts to rehabilitate her remaining small bowel included reduction in total TPN calories, redistribution of macronutrients, a 6-week trial of growth hormone supplementation, provision of gut-specific fuels, insertion of a gastric tube, and temporary discontinuation of TPN, which was complicated by dehydration and diarrhea. The patient's weight dropped from 75 to 50 kg, and her serum bilirubin remained elevated. Fifteen months after discontinuing copper supplementation, the patient required transfusion with 2 units of red cells for symptomatic anemia (Fig. 1, day 1). There was no clinical or laboratory evidence of acute blood loss, hemolysis, or deficiency of iron, folic acid, or vitamin B_{12}. Over the next few months her white blood cell (WBC) and platelet counts steadily declined, and she required monthly infusions of 2 units of red cells.

One hundred eight days after the patient's first red cell transfusion, she complained of a severe headache and fever. Bacterial endocarditis with systemic embolization was confirmed by echocardiogram (aortic valve vegetation and aortic insufficiency), computed tomography (CT) scan (a left temporoparietal infarction), and blood cultures positive for *Klebsiella pneumonia* and *Enterococcus faecalis*. A biliary source for her bacteremia was suspected based on the type of pathogens. The patient did not use illicit IV drugs, and cultures of her TPN central catheter tip after removal showed no growth. The patient responded rapidly to antibiotic treatment with vancomycin and gentamicin. There was a brief improvement in both WBC and platelet count (days 109 to 116), followed by a steep decline. The interval between red cell transfusions decreased to every 2 to 3 weeks despite rapid clinical improvement.

Nineteen months after discontinuing TPN copper supplementation (Fig. 1, day 131), a bone marrow biopsy was performed that showed a normocellular marrow, adequate numbers of megakaryocytes, and a relative erythroid hyperplasia (myeloid:erythroid ratio, 1.5:1; normal, 3:1). Myeloid maturation was arrested, and some myeloid and erythroid precursors contained large, abnormal vacuoles. Stainable iron was present, and abnormal accumulation of iron within maturing nucleated red cells (sideroblasts) was not identified.

Copper deficiency, suspected as a possible cause of the patient's neutropenia, thrombocytopenia, and worsening anemia, was confirmed when serum copper (25 μg/dL; normal, 70 to 155 μg/dL) and ceruloplasmin (7.1 mg/dL; normal, 15 to 60 mg/dL) concentrations were obtained (Fig. 1, day 133). A standard trace element formulation containing 1 mg of elemental copper was added daily to the TPN. Over the next 6 weeks serum copper levels rose, and the patient's neutropenia and thrombocytopenia improved rapidly. Two weeks after copper supplementation was begun, she was transfused two units of red cells for a hematocrit of 21%. Thereafter, the patient did not require red cell transfusion support for 124 days.

Copper supplementation was discontinued when the

patient's serum copper rose to 186 μg/dL (Fig. 1, day 174). Over the next 3 months, serum copper concentration rapidly declined, reaching a nadir of 10 μg/dL (Fig. 1, day 272), concurrent with worsening neutropenia, thrombocytopenia, and anemia, and necessitating red cell transfusions. After reinstatement of copper supplementation, serum copper concentration, and neutrophil and platelet counts rebounded.

Shortly thereafter, the patient began to decline steadily, secondary to progressive cardiac failure due to severe mitral regurgitation and aortic valve insufficiency after endocarditis and portal hypertension. A third liver biopsy confirmed marked worsening of hepatic fibrosis, inflammation, and steatosis. New complications included intractable ascites, hepatic encephalopathy, and spontaneous intraperitoneal hemorrhages. Multiple abdominal imaging techniques (CT scan, ultrasound, visceral angiogram, and ERCP), and direct observation during exploratory laparotomy confirmed splenomegaly of recent onset and patency of hepatic and portal veins. The patient died 4 months after copper was restored to her TPN for the second time.

DISCUSSION

A causal relationship between copper deficiency and anemia, neutropenia, and thrombocytopenia was confirmed in this patient by documenting pancytopenia and hematopoietic recovery corresponding to hypocupremia and its correction after addition of copper to TPN on two separate occasions.

Copper is an essential trace element, third in total body content after iron and zinc, and is widely distributed throughout human tissues and organs, reaching the highest concentrations in the liver.[5] All metalloenzymes of copper possess oxidative reductase activity. Examples include cross-linking of connective tissue (lysl oxidase), reduction of O_2^- (Cu/Zn superoxide dismutase), mitochondrial respiration (cytochrome C oxidase), and oxidation of iron from ferrous to ferric state (ceruloplasmin).[1]

Numerous physiologic roles of copper have been identified from studies of nonhuman mammals[6] and inherited copper deficiency states such as Menke's kinky hair syndrome.[7] A partial list of the functions of copper includes hematopoiesis, myelin formation, melanin pigment synthesis, connective tissue synthesis, skeletal mineralization, and immune function.[1,4,5] However, the exact role or identity of cuproenzymes involved in many of these functions is unknown or uncertain. This is especially true for hematopoiesis. A complete understanding of copper regulation is also lacking. Absorption apparently can occur in the stomach and throughout the small intestine, and both active and passive transport mechanisms may be involved.[5] Although most plasma copper is bound to ceruloplasmin, copper transport from the intestinal mucosa to liver and other tissues is poorly understood.[1] The primary route of copper excretion is biliary and is estimated to approximate 1.2 mg/d.[7] Conditions leading to chronic biliary obstruction impair copper excretion and may promote hepatic accumulation.[2] Whether excess hepatic copper contributes to TPN-associated liver disease is unknown; however, recommendations to reduce or eliminate copper from TPN in patients with hyperbilirubinemia were the basis for our decision to withhold copper from our patient's TPN.

Recommendations for dietary copper intake range from 1.55 to >2.0 mg/d.[7] Because of the ubiquitous presence of copper in the diet (highest in shell fish, nuts, legumes, and grains), it is extremely difficult to become copper deficient if adequate caloric intake is maintained, with the exception of infants and children who are exclusively fed cow's milk.[8] The American Medical Association recommendation for parenteral nutrition supplementation of copper is 0.5 to 1.5 mg/d.[9] Fleming[3] recommended reducing copper supplementation in TPN to 0.15 mg/d when a patient develops chronic hyperbilirubinemia. Reduction of a single trace element can be problematic because trace elements are generally added as a preparation containing several trace elements. Therefore, it may be more clinically feasible to reduce copper supplementation by providing a trace element preparation no more than three times a week when a patient develops chronic hyperbilirubinemia.[10] Factors contributing to inadequate absorption of dietary copper in our patient were intestinal resection with reduced absorptive capacity and rapid gastrointestinal transit (transit time from gastric emptying to ileocecal valve was 3 minutes). Rarer conditions associated with acquired copper deficiency include excessive oral zinc supplementation[11,12] (zinc interferes with transport of copper out of intestinal mucosal epithelium), intestinal malabsorption syndromes,[13] and chronic renal failure.[14]

Table I summarizes the clinical features of TPN-associated copper deficiency contained in 14 published case reports, including our patient. All patients required long-term TPN because of congenital or acquired small bowel disorders, except for one patient with esophageal cancer. Anemia (n = 1), neutropenia (n = 5), or both (n = 8) were the first signs of copper deficiency after an average duration of 11 months receiving TPN lacking copper supplementation. The variable time to onset of hematologic signs of copper deficiency most likely reflects differences between patients in terms of enteral absorption, excretion, and total body storage of copper.

Thrombocytopenia occurred in three cases. Wasa et al[23] reported a 69-year-old woman with prolonged postoperative small bowel obstruction whose platelet count nadired at 82,000/μL after 10 months of TPN, increasing to 221,000/μL after 2 weeks of parenteral copper. Spiegel and Willenbucher[24] described a patient with Crohn's disease, short bowel syndrome, cholestasis, and intra-abdominal sepsis whose platelet counts dropped to 97,000 to 125,000/μL after withholding copper and rose to >200,000/μL after copper was added to TPN. Our patient's platelet count fell to 83,000/μL during the first period of hypocupremia and to 27,000/μL when her serum copper declined a second time. Despite concurrent medical complications, the WBC, absolute neutrophil count (ANC), and platelet nadirs preceded parenteral copper supplementation and normalization of serum copper. Mild thrombocyto-

TABLE I
Hematologic complications of TPN-related copper deficiency

Reference	Year	Age (y)	Condition requiring TPN	Duration of TPN (mo)*	Nadir Cu (μg/dL)†	Anemia	Neutropenia	Thrombocytopenia	Rechallenged	Bone marrow findings
15	1972	<1	Ileal atresia	7	9	Y	Y	NR	N	A, F
16	1974	45	Small bowel infarction	18	11	Y	Y	N	Y	A, B, C, F, G
		12	Small bowel infarction	11	32	N	Y	NR	N	A, B
17	1974	37	Small bowel infarction	?	13	Y	Y	NR	N	
18	1974	56	Small bowel dismotility	3	2	Y	Y	N	N	A, D
19	1977	30	Small bowel infarction	1	27	Y	Y	N	Y	A, B, C, E, G
20	1986	56	Gastrocolic anastomosis	14	5	N	Y	NR	N	
21	1989	18	Enterocutaneous fistula	7	3	Y	Y	NR	N	
		48	Crohn's disease	4	4	N	Y	NR	Y	
		68	Esophageal cancer	11	6	N	Y	NR	N	
22	1992	68	Postgastrectomy malabsorption	30	2	Y	Y	N	N	A, B, C, D
23	1994	69	Small bowel obstruction	15	10	Y	Y	Y	N	
24	1999	32	Crohn's disease	2	17	Y	Y	Y	N	B, D, G
This report	1999	39	Small bowel infarction	19	25	Y	Y	Y	Y	A, B

Y, yes; N, no; NR, not reported; A, myeloid arrest; B, vacuoles in myeloid and/or erythroid precursors; C, sideroblasts; D, hypocellular; E, hypercellular; F, hypochromic; G, megaloblastoid.
*Months from start of TPN until copper deficiency was diagnosed.
†Typical reference range, 70–155 μg/dL.

penia (92,000/μL) was also noted in a copper-deficient patient with chronic renal failure receiving a "modified" diet, whose pancytopenia responded to oral copper supplementation.[14]

A wide range of morphologic changes on peripheral blood smears and bone marrow biopsies has been reported in association with copper deficiency.[7] Red cells are described as microcytic, normocytic,[15] or macrocytic,[8,16] and hemoglobin content as hypochromic.[15,21] Reticulocyte count, when reported, is low.[15,16,19] Some erythrocyte variation may be due to coexisting deficiencies of iron or folate, but this is not documented in most cases. Bone marrow morphologic findings are also variable. However, there are two consistent findings: a relative absence of mature myeloid cells (bands and segmented neutrophils), and cytoplasmic vacuoles in myeloid and erythroid precursors, present in 7 of 8 and 6 of 8, respectively, of the bone marrow findings described in Table I. Similar cytoplasmic vacuoles have been reported in patients with acute alcohol intoxication or chloramphenicol toxicity and after chemotherapy.[11] The exact mechanism by which impaired copper-dependent functions are involved in myeloid arrest is unknown. However, it does not seem to be due to Cu/Zn superoxide dismutase or Cu cytochrome oxidase deficiencies.[26] In three cases, the bone marrow contained ringed sideroblasts (maturing nucleated red cells containing abnormal granules that stain positive for iron). This suggests a copper-dependent defect of iron incorporation into hemoglobin, but the precise mechanism is unknown. Copper deficiency–associated disorders of bone marrow platelet production rarely have been described.[11,24] However, quantitative and qualitative abnormalities of megakaryocytes, the precursor cell of platelets, are frequently subtle and subjective.

In conclusion, copper deficiency can develop in patients with short bowel syndrome and TPN-induced biliary obstruction, despite continued ingestion of copper-containing foods. The earliest sign of copper deficiency is peripheral blood cytopenias, typically anemia and neutropenia, and occasionally, thrombocytopenia. Decreased bone marrow production, rather than increased peripheral destruction, of erythrocytes, neutrophils, and platelets appears to be the primary cause. Determining the different copper dependent enzymes involved in hematopoiesis requires further investigation. Before withholding or diminishing copper supplementation from the parenteral TPN in patients with hyperbilirubinemia, copper concentrations should be measured.[24] If the serum copper level is elevated and copper in TPN is withheld or reduced, frequent monitoring is necessary to avoid the consequences of iatrogenic copper deficiency. On the basis of our experience with this patient, we have adopted the following policy: monitor serum copper quarterly and provide a standard trace element preparation three times a week, adjusting the frequency in response to serum copper levels.

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