

Neutropenia and anaemia secondary to copper deficiency in a child receiving long-term jejunal feeding: a case report

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Case report

In January 2017, a girl was born full term to non-consanguineous Chinese parents. Oesophageal atresia with a distal tracheo-oesophageal fistula was diagnosed soon after birth. Emergency surgical repair was attempted on day 1 of life but was complicated by complete transection of the left main bronchus that was subsequently repaired. The tracheo-oesophageal fistula was divided and a gastrostomy created. End-to-end anastomosis of the proximal and distal oesophagus was performed at age 6 months. Gastrostomy feeding was switched to jejunal feeding at 7 months because of gastroesophageal reflux and recurrent aspiration pneumonia. Attempted fundoplication at 17 months failed due to a small tubular stomach. She was prescribed oral ranitidine 30 mg three times daily.

At birth, the child's haematology results were normal but by age 2 years she had developed persistent severe neutropenia (lowest neutrophil count $0.13 \times 10^9/L$) and microcytic anaemia, with a lowest haemoglobin of 6.6 g/dL and lowest mean corpuscular volume of 65.5 fL. Platelet count was normal and she had no major infection or signs of anaemia. She was on continuous jejunal feeding with high-energy infant formula (Infatrini; Nutricia, Zoetermeer, The Netherlands) 640 mL daily as well as iron(III)-hydroxide polymaltose complex (IPC) 25 mg daily and multivitamin drops (Poly-Vi-Sol; Mead-Johnson Nutrition, Chicago [IL], United States) 1 mL daily. The high-energy infant formula provided 416 µg of copper daily, equivalent to 1.2 times the recommended dietary allowance.

Growth was satisfactory with her body weight at the 25th centile and height at the 10th centile. No new physical sign was detected. Peripheral blood smear showed occasional macro-ovalocytes. A dimorphic red cell picture was not seen and there were no hypersegmented neutrophils. Serum iron of 4.6 µmol/L (normal, 4-25 µmol/L), total iron-binding

capacity of 103 µmol/L (normal, 41-77 µmol/L), and transferrin saturation of 4% (normal, 7%-44%) were suggestive of iron deficiency. Haemoglobin pattern analysis was negative for thalassaemia. Serum active vitamin B12 level was low at 23.6 pmol/L (normal, >46.2 pmol/L) and serum and red blood cell folate, serum bilirubin and lactate dehydrogenase levels were normal. Direct antiglobulin test, antinuclear antibody, C3, C4, anti-intrinsic factor antibody, antiparietal cell antibody and antineutrophil antibody were all negative.

Intramuscular vitamin B12 was given and ranitidine was stopped. The dose of IPC was increased to 15 mg twice daily and administered via the gastric tube.

Despite normalisation of serum iron and vitamin B12 level, anaemia and neutropenia persisted. Haemoglobin further dropped to 6.6 g/dL and red blood cell transfusion was required. She responded to a dose of granulocyte colony-stimulating factor with the neutrophil count rising from $0.25 \times 10^9/L$ to $1.74 \times 10^9/L$. Nonetheless, her neutrophil count dropped to $0.33 \times 10^9/L$ 5 days later. Bone marrow aspiration and trephine biopsy was performed to evaluate the cause of refractory cytopenias and revealed reduced granulopoiesis, reactive histiocytosis and iron block. Vacuolated myeloid and erythroid precursors were observed (Fig 1). Megakaryopoiesis was adequate and no sideroblasts were evident on iron staining. These findings suggested copper deficiency or zinc toxicity. Serum copper was subsequently found to be <2.0 µmol/L (normal, 13-24 µmol/L), consistent with severe copper deficiency, whilst serum zinc level was normal.

Copper deficiency was treated with mineral mixture powder (Seravit; Nutricia) via the gastric tube from age 28 months as direct copper supplement was not available. The mineral mixture powder was administered at a dose of 2.5 g daily, providing

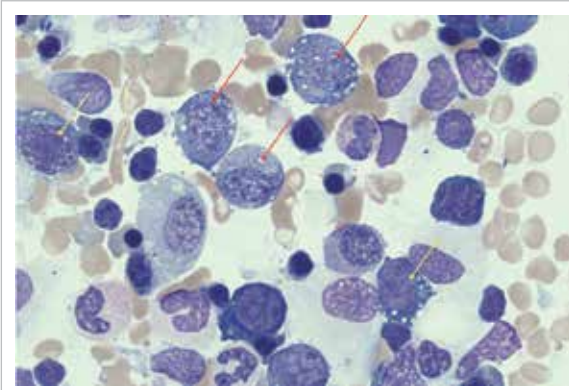


FIG 1. A 28-month-old girl with neutropenia and anaemia. Bone marrow aspirate showing vacuolated myeloid precursors (red arrows) and vacuolated erythroid precursors (yellow arrows)

12.2 g/dL; absolute neutrophil count, $2.03 \times 10^9/L$) and by 7 weeks, serum copper had normalised. The mineral mixture powder was stopped after 8 weeks, at age 30 months. At age 35 months, haemoglobin, neutrophil count, copper, and iron levels remained normal (Fig 2).

Discussion

The index patient presented with haematological abnormalities due to acquired copper deficiency following long-term jejunal feeding, which is not well reported in the literature.¹ Jacobson et al² reported three paediatric patients with exclusive jejunal feeding who developed cytopenias, one of whom had concurrent combined iron and vitamin B12 deficiency similar to our patient. Premature infants and children with intestinal failure on parenteral nutrition with inadequate copper supplementation are also at increased risk of acquired copper deficiency.³

Although the amount of iron, copper and vitamin B12 provided was above the recommended dietary requirement, deficiencies occurred because of problems in absorption. Most copper absorption occurs in the stomach and proximal duodenum. The acidic environment in the stomach facilitates solubilisation by dissociating it from copper-containing dietary macromolecules. Jejunal administration of IPC, multivitamin drops and infant formula bypassed the stomach and ranitidine reduced the acidity of the jejunal environment.

Copper-dependent enzymes are essential for normal function of the haematopoietic, skeletal, and central nervous systems. Although absent in the index patient, clinical signs of copper deficiency such as fragile, abnormally formed hair, depigmentation of the skin, oedema, myeloneuropathy, ataxia and cognitive deficits should be actively sought. Anaemia and neutropenia are the predominant haematological manifestations. Thrombocytopenia rarely occurs. Serum ferritin and erythropoietin are usually elevated. Serum ceruloplasmin is low. Anaemia is caused by the reduced activity of ceruloplasmin ferroxidase, copper/zinc superoxidase and cytochrome-c oxidase.⁴ Upon copper supplementation, neutropenia typically improves within a few weeks and anaemia improves within a few months. Cytoplasmic vacuolation in erythroid and myeloid precursors is the prominent feature in the bone marrow. Dysplastic features, such as megaloblastic changes and ring sideroblasts, may be observed.⁴ Vacuolated erythroblasts and myeloid precursors are classically observed in Pearson syndrome,⁵ acute alcoholism, chloramphenicol and linezolid toxicity, acute erythroid leukaemia and acute metabolic disturbance. These causes were unlikely in the index patient in the absence of an associated history or pathological features. Primary

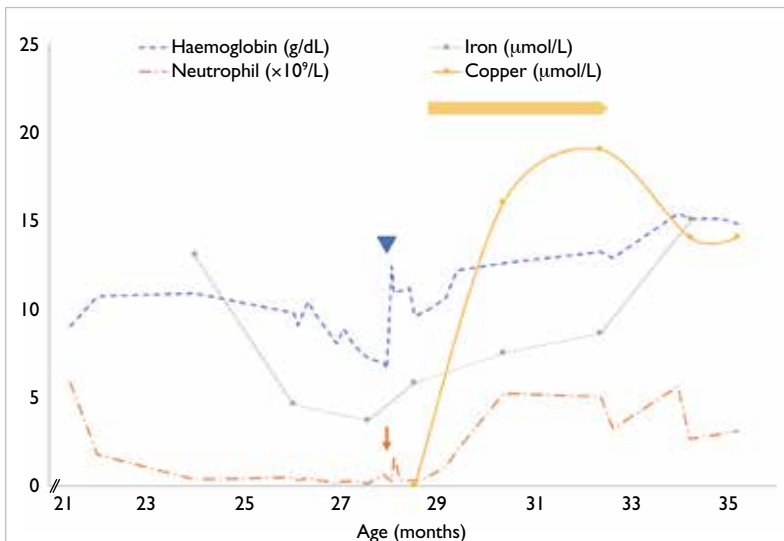


FIG 2. Haemoglobin, neutrophil, iron, and copper levels in a girl with neutropenia and anaemia. At age 26 months, iron(III)-hydroxide polymaltose complex (IPC) was increased from 10 mg daily to 10 mg twice daily via a jejunostomy tube. At age 27 months, IPC was increased to 15 mg twice daily via a gastrostomy tube. Blood transfusion (blue arrowhead) and granulocyte colony-stimulating factor (orange arrow) were given at age 28 months. Mineral mixture powder was given from age 28 months to 30 months (yellow arrow)

115 μg copper each day. On day 9 after commencement of copper supplementation, the absolute neutrophil count increased from the lowest level of $0.29 \times 10^9/L$ to $1.09 \times 10^9/L$ and haemoglobin level increased from the lowest level of 9.6 g/dL to 10.6 g/dL. The mineral mixture powder was further increased to 2.5 g twice daily. A small amount of milk was introduced to the stomach to allow absorption of the micronutrients. On day 16, the haemoglobin and neutrophil count normalised (haemoglobin,

myelodysplasia is an important differential diagnosis but blood count recovery on copper replacement would not be expected.

This case highlights the importance of nutritional monitoring in patients receiving exclusive jejunal feeding. We recommend checking full blood count, liver and renal function tests, electrolytes, iron profile, vitamin B12, copper and zinc level every 3 months. Unexplained anaemia or neutropenia should prompt investigations for possible micronutrient deficiency to avoid unnecessary invasive investigations.

Author contributions

Concept or design: All authors.

Acquisition of data: WY Leung, CC So.

Analysis or interpretation of data: WY Leung.

Drafting of the manuscript: WY Leung, CC So.

Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The parent of the patient provided written consent for publication.

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