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**REVIEW**

- 8627 Time to give up traditional methods for the management of gastrointestinal neuroendocrine tumours  
*Yozgat A, Kekilli M, Altay M*

**MINIREVIEWS**

- 8647 Healthcare practice strategies for integrating personalized medicine: Management of COVID-19  
*Liu WY, Chien CW, Tung TH*
- 8658 Clinical application of repetitive transcranial magnetic stimulation for post-traumatic stress disorder: A literature review  
*Cheng P, Zhou Y, Xu LZ, Chen YF, Hu RL, Zou YL, Li ZX, Zhang L, Shun Q, Yu X, Li LJ, Li WH*
- 8666 Pros and cons of continuous glucose monitoring in the intensive care unit  
*Sun MT, Li IC, Lin WS, Lin GM*

**ORIGINAL ARTICLE****Clinical and Translational Research**

- 8671 Prognostic implications of ferroptosis-associated gene signature in colon adenocarcinoma  
*Miao YD, Kou ZY, Wang JT, Mi DH*

**Retrospective Study**

- 8694 Cefoperazone sodium/sulbactam sodium *vs* piperacillin sodium/tazobactam sodium for treatment of respiratory tract infection in elderly patients  
*Wang XX, Ma CT, Jiang YX, Ge YJ, Liu FY, Xu WG*
- 8702 Modified Gant procedure for treatment of internal rectal prolapse in elderly women  
*Xu PP, Su YH, Zhang Y, Lu T*
- 8710 Clinical and imaging features of desmoid tumors of the extremities  
*Shi Z, Zhao XM, Jiang JM, Li M, Xie LZ*
- 8718 Retrospective analysis of surgically treated pT4b gastric cancer with pancreatic head invasion  
*Jin P, Liu H, Ma FH, Ma S, Li Y, Xiong JP, Kang WZ, Hu HT, Tian YT*
- 8729 Development of a random forest model for hypotension prediction after anesthesia induction for cardiac surgery  
*Li XF, Huang YZ, Tang JY, Li RC, Wang XQ*

**Clinical Trials Study**

- 8740** Effects of mindful breathing combined with sleep-inducing exercises in patients with insomnia  
*Su H, Xiao L, Ren Y, Xie H, Sun XH*

**Observational Study**

- 8749** Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality  
*Ronderos D, Omar AMS, Abbas H, Makker J, Baiomi A, Sun H, Mantri N, Choi Y, Fortuzi K, Shin D, Patel H, Chilimuri S*
- 8763** Midazolam dose is associated with recurrence of paradoxical reactions during endoscopy  
*Jin EH, Song JH, Lee J, Bae JH, Chung SJ*

**CASE REPORT**

- 8773** Isolated mass-forming IgG4-related sclerosing cholangitis masquerading as extrahepatic cholangiocarcinoma: A case report  
*Song S, Jo S*
- 8782** *Samonella typhi* infection-related appendicitis: A case report  
*Zheng BH, Hao WM, Lin HC, Shang GG, Liu H, Ni XJ*
- 8789** ACTA2 mutation is responsible for multisystemic smooth muscle dysfunction syndrome with seizures: A case report and review of literature  
*Yang WX, Zhang HH, Hu JN, Zhao L, Li YY, Shao XL*
- 8797** Whole-genome amplification/preimplantation genetic testing for propionic acidemia of successful pregnancy in an obligate carrier Mexican couple: A case report  
*Neumann A, Alcantara-Ortigoza MA, González-del Angel A, Zarate Díaz NA, Santana JS, Porchia LM, López-Bayghen E*
- 8804** Is mannitol combined with furosemide a new treatment for refractory lymphedema? A case report  
*Kim HS, Lee JY, Jung JW, Lee KH, Kim MJ, Park SB*
- 8812** Successful treatment of floating splenic volvulus: Two case reports and a literature review  
*Sun C, Li SL*
- 8820** Removal of "ruptured" pulmonary artery infusion port catheter by pigtail catheter combined with gooseneck trap: A case report  
*Chen GQ, Wu Y, Zhao KF, Shi RS*
- 8825** Isolated neutropenia caused by copper deficiency due to jejunal feeding and excessive zinc intake: A case report  
*Ohmori H, Kodama H, Takemoto M, Yamasaki M, Matsumoto T, Kumode M, Miyachi T, Sumimoto R*
- 8831** Diagnosis and treatment of eosinophilic fasciitis: Report of two cases  
*Song Y, Zhang N, Yu Y*
- 8839** Familial left cervical neurofibromatosis 1 with scoliosis: A case report  
*Mu X, Zhang HY, Shen YH, Yang HY*

- 8846** Successful treatment after toxic epidermal necrolysis induced by AZD-9291 in a patient with non-small cell lung cancer: A case report  
*Li W, He X, Liu H, Zhu J, Zhang HM*
- 8852** Anesthesia management in a pediatric patient with Becker muscular dystrophy undergoing laparoscopic surgery: A case report  
*Peng L, Wei W*
- 8858** Diagnosis of upper gastrointestinal perforation complicated with fistula formation and subphrenic abscess by contrast-enhanced ultrasound: A case report  
*Qiu TT, Fu R, Luo Y, Ling WW*
- 8864** Adenomyoepithelioma of the breast with malignant transformation and repeated local recurrence: A case report  
*Oda G, Nakagawa T, Mori M, Fujioka T, Onishi I*
- 8871** Primary intracranial synovial sarcoma with hemorrhage: A case report  
*Wang YY, Li ML, Zhang ZY, Ding JW, Xiao LF, Li WC, Wang L, Sun T*
- 8879** Lumbar infection caused by *Mycobacterium paragordoniae*: A case report  
*Tan YZ, Yuan T, Tan L, Tian YQ, Long YZ*
- 8888** Primary intratracheal neurilemmoma in a 10-year-old girl: A case report  
*Wu L, Sha MC, Wu XL, Bi J, Chen ZM, Wang YS*
- 8894** Ovarian pregnancy rupture following ovulation induction and intrauterine insemination: A case report  
*Wu B, Li K, Chen XF, Zhang J, Wang J, Xiang Y, Zhou HG*
- 8901** Delayed diagnosis of imperforate hymen with huge hematocolpometra: A case report  
*Jang E, So KA, Kim B, Lee AJ, Kim NR, Yang EJ, Shim SH, Lee SJ, Kim TJ*
- 8906** Acute pancreatitis with hypercalcemia caused by primary hyperparathyroidism associated with paraneoplastic syndrome: A case report and review of literature  
*Yang L, Lin Y, Zhang XQ, Liu B, Wang JY*
- 8915** Use of a modified tracheal tube in a child with traumatic bronchial rupture: A case report and review of literature  
*Fan QM, Yang WG*
- 8923** Isolated liver metastasis detected 11 years after the curative resection of rectal cancer: A case report  
*Yonenaga Y, Yokoyama S*
- 8932** Severe bleeding after operation of preauricular fistula: A case report  
*Tian CH, Chen XJ*
- 8938** Secondary aorto-esophageal fistula initially presented with empyema after thoracic aortic stent grafting: A case report  
*Wang DQ, Liu M, Fan WJ*

- 8946** Disruption of sensation-dependent bladder emptying due to bladder overdistension in a complete spinal cord injury: A case report

*Yoon JY, Kim DS, Kim GW, Won YH, Park SH, Ko MH, Seo JH*

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## Isolated neutropenia caused by copper deficiency due to jejunal feeding and excessive zinc intake: A case report

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### Abstract

#### BACKGROUND

Percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) is often used to treat patients with neurological impairment and difficulty in swallowing. However, these patients often develop copper deficiency. This report describes a case of isolated neutropenia, which is a rare manifestation of copper deficiency.

#### CASE SUMMARY

Our patient was a 19-year-old boy with neurological impairment and gastroesophageal reflux. He received PEG-J feeding, including an enteral supplement containing copper and zinc. However, as his serum zinc level was low (53 µg/dL) at the age of 19 years and 2 mo, we changed to a zinc-rich supplement containing 22 mg/d of zinc and 1.0 mg/d of copper. The supplement comprised a mixture of isocal 1.0 junior (5 packs/d), Tezon [2 packs (250 mL)/d], and cocoa powder. Seven months later, he had neutropenia (606/mm<sup>3</sup>) with a serum copper level of 16 µg/dL. There were no other manifestations of copper deficiency, including anemia. Copper deficiency and neutropenia both improved following the

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administration of cocoa powder and Tezon.

## CONCLUSION

In patients receiving long-term PEG-J feeds, white blood cell counts, hemoglobin, and serum levels of copper and zinc should be regularly monitored.

**Key Words:** Percutaneous endoscopic gastrostomy with jejunal extension feeding; Neutropenia; Copper; Zinc; Deficiency; Case report

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**Core Tip:** Patients with percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) often develop copper deficiency. Approximately 2 mg/d of copper may be needed to prevent deficiency. The intake ratio of copper to zinc is critical for maintaining an adequate serum copper concentration. We report an isolated case of neutropenia caused by copper deficiency in a patient with neurological impairment receiving PEG-J feeding with additional supplementation of zinc. Copper deficiency improved with the addition of cocoa powder to the enteral formula.

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## INTRODUCTION

Patients with neurological impairment often experience difficulty in swallowing. They also often experience gastroesophageal reflux (GER), which induces reflux esophagitis and aspiration pneumonia[1]. Percutaneous endoscopic gastrostomy (PEG) and fundoplication are used to treat these conditions that are associated with prolonged enteral feeding in such patients[2]. Jejunal tube feeding by PEG with jejunal extension (PEG-J) is also used to treat GER in these patients[3-5]. However, patients receiving PEG-J feeding occasionally develop deficiencies in trace elements, including copper[6-9]. We report an isolated case of neutropenia caused by copper deficiency in a patient with neurological impairment receiving PEG-J feeding. The copper deficiency was improved by the addition of cocoa powder to the enteral formula.

## CASE PRESENTATION

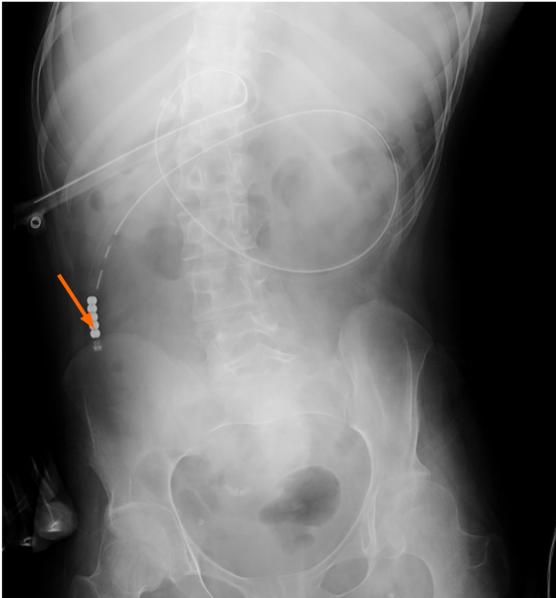
### Chief complaints

Nutritional care.

### History of present illness

At the age of 16 years, upper gastrointestinal examination revealed that he had complicated GER. During an examination, he accidentally suffered a cardiac-respiratory arrest. After resuscitation, he was bedridden with spastic quadriplegia and difficulty in swallowing.

At the age of 18, a PEG-J catheter was inserted in the proximal jejunum 60 cm from the gastrostomy site for nutrition (Figures 1 and 2). The catheter tip was located 4 cm below the ligament of Treitz. An enteral formula containing Lacol (900 mL/d) and BFLUID (500 mL/d) was administered, which provided 1260 kcal, 1.1 mg of copper, and 5.8 mg of zinc per day. At the age of 19 years and 2 mo, a low serum level of zinc [53 µg/dL (normal range: 80-130 µg/dL)] was detected. Therefore, we replaced the enteral formula with a zinc-rich one containing isocal 1.0 junior (Nestle Health Science, Tokyo; 5 packs/d) and VCRESC CP-10 (NUTRI Co., Ltd., Mie; 1 pack/d), which provided 1080 kcal, 1.0 mg of copper, and 22.0 mg of zinc (zinc to copper ratio: 22:1)



**Figure 1** Radiograph confirming the proper placement of the percutaneous endoscopic gastrostomy with jejunal extension catheter's tip in the upper jejunum (arrow).



**Figure 2** X-ray findings after the infusion of the contrast medium (gastrograffin) through the percutaneous endoscopic gastrostomy with jejunal extension catheter. The contrast medium is visible from the upper jejunum to the lower part of the small intestine. However, it is not observed in the reflux to the duodenum.

per day.

#### **History of past illness**

The patient was a 19-year-old boy diagnosed with xeroderma pigmentation type A based on the clinical manifestations and analysis of XPA 9q34.1. Due to neurological impairment, his motor development was delayed. He also developed GER.

#### **Personal and family history**

The patient did not have a remarkable family history.

#### **Physical examination**

At the age of 19 years and 4 mo, he was admitted to our hospital. On admission, the patient's height was 152 cm, and he was appreciably underweight at 35 kg. The patient was bedridden, non-verbal, unable to sit upright, roll over, or walk. Intermittent urine

catheterization had been performed due to neurogenic bladder. Mental retardation was severe and IQ was presumed < 35. His respiratory and heart sounds were normal. The abdomen was soft and nondistended.

### Laboratory examinations

As shown in [Table 1](#), at admission, his neutrocyte count was 2475/mm<sup>3</sup>, and the serum levels of copper and zinc were 111 µg/dL and 53 µg/dL, respectively. As the serum zinc level was still low, the same enteral formula was continued. However, at the age of 19 years and 9 mo, the patient developed neutropenia (606/mm<sup>3</sup>) ([Table 1](#)). His red blood cell and platelet counts, hemoglobin, and serum levels of zinc and selenium were all normal. However, the serum levels of copper and ceruloplasmin were significantly decreased to 16 µg/dL and 4.6 mg/dL (normal range: 21-37 mg/dL), respectively.

### Imaging examinations

Figures 1 and 2 present the radiographs that were obtained when the PEG-J catheter was inserted at the age of 18 years; these confirm the proper placement of the catheter's tip in the upper jejunum and the infusion of the contrast medium (gastrograffin) through the catheter, respectively. The contrast medium was noted from the upper jejunum to the lower portion of the small intestine.

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## FINAL DIAGNOSIS

He was diagnosed with neutropenia due to copper deficiency. No other symptoms of copper deficiency, such as hair abnormalities, were observed.

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## TREATMENT

To treat the copper deficiency, the enteral formula was changed to a mixture of isocal 1.0 junior (5 packs/d), Tezon [TERUMO Co., Ltd., Tokyo; 2 packs (250 mL)/d], and cocoa powder [Morinaga & Co., Ltd, Tokyo; 2 spoons (10 g of cocoa)/d]. Tezon is a supplement of trace elements containing zinc (8.0 mg/250 mL) and copper (0.6 mg/250 mL). Ten grams of cocoa powder contained 0.7 mg of zinc and 0.38 mg of copper.

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## OUTCOME AND FOLLOW-UP

The new enteral formula provided 1076 kcal, 1.98 mg of copper, 18.0 mg of zinc (zinc to copper ratio: 18:1.98). Two months later, the neutrocyte count and serum levels of copper and ceruloplasmin were normal, as shown in [Table 1](#). The serum C-reactive protein level was negative during this period.

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## DISCUSSION

Copper deficiency is caused by jejunal feeding, low copper intake, excessive zinc intake, the malabsorption syndrome, and parenteral nutrition[10]. When our patient developed copper deficiency, his copper intake of 1 mg/d was in line with the recommended daily allowance of 0.9 mg/d for men aged 18-29 years old[11].

Copper is absorbed in two phases: The early phase occurs in the stomach and the proximal duodenum, while the delayed phase occurs in the distal duodenum and the small intestine[6,7].

[Figure 2](#) clearly shows the contrast flowing from the catheter into the upper jejunum and below, but no contrast was seen in the reflux to the duodenum. These findings indicated that copper from the enteral formula was not absorbed in the stomach and the duodenum, leading to its deficiency.

In our patient, the nutritional formula was changed to a zinc-rich preparation 3 mo prior to the onset of neutropenia. While the recommended ratio of zinc: copper intake is 5-10:1[12], our enteral formula had a much higher ratio of 22:1. Excessive zinc intake has been shown to induce copper deficiency through the induction of metallothionein,

Table 1 Laboratory data

Age		19 yr 4 mo	19 yr 6 mo	19 yr 9 mo	19 yr 10 mo	19 yr 11 mo
	RDA <sup>1</sup>					
Cu intake (mg/d)	0.9	1.0	1.0	1.98	1.98	1.98
Zn intake (mg/d)	11	22	22	18	18	18
Kcal		1080	1080	1076	1076	1076
	Normal ranges					
WBC (/mm <sup>3</sup> )	3300-8600	5000	4800	2900	3700	4200
Neutrocyte (/mm <sup>3</sup> )		2475	1786	606	1166	1865
RBC × 10 <sup>4</sup> (/mm <sup>3</sup> )	435-555	468	489	468	464	486
Hb (g/dL)	13.7-16.8	13.6	14.6	14.4	14.5	15.0
Platelets × 10 <sup>4</sup> (/mm <sup>3</sup> )	15.8-34.8	28.5	18.8	18.8	21.6	20.0
Cu (µg/dL)	66-130	111	65	16	92	116
Zn (µg/dL)	80-130	53		106	86	70
Se (µg/dL)	10.6-17.4	92		99	109	84
Fe (µg/dL)	54-181	64	93		80	93
Ferritin (ng/mL)	25-280	54			111	96
Ceruloplasmin(mg/dL)	21-37	15.9		4.6	19.5	20.4

<sup>1</sup>Recommended dietary allowance at the age of 18-29 years[11]. RDA: Recommended dietary allowance; Cu: Copper; Zn: Zinc; Kcal: Kilocalorie; WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Se: Selenium; Fe: Iron.

an endogenous metal chelator with a higher affinity to copper than to zinc. An increase in metallothionein levels further inhibits enteric copper absorption in the intestinal epithelial cells[13]. Thus, the ratio of zinc to copper is critical for preventing copper deficiency. Therefore, copper deficiency in our patient could have been caused by the combination of PEG-J feeding and excessive zinc intake.

Copper is an essential trace element that functions as a cofactor for several enzymes, including cytochrome C oxidase, dopamine β-hydroxylase, lysyl oxidase, and ceruloplasmin. Copper deficiency leads to a decrease in the activities of these enzymes, resulting in various manifestations of the deficiency, including hair abnormalities, osteoporosis, and neurological dysfunction (such as sensory ataxia and peripheral neuropathy)[14-16]. Copper deficiency also results in hematological abnormalities[8, 17,18].

Halfdanarson *et al*[17], in a study of 40 patients, reported the hematological manifestations of copper deficiency. While 52.5% of the patients had anemia and leukopenia, 30% only had anemia, 10% had pancytopenia, 5% had anemia and thrombocytopenia, and only one patient had isolated neutropenia. Therefore, isolated neutropenia, as seen in our patient, is a rare manifestation of copper deficiency.

Neutropenia and anemia caused by copper deficiency have different etiologies. Anemia due to copper deficiency is caused by the inhibition of ferroxidase copper-dependent enzymes[18], resulting in impaired hemoglobin synthesis. In contrast, copper deficiency-induced neutropenia is speculated to be caused by the destruction of myeloid progenitor cells in the bone marrow, impaired maturation of myeloid precursors, and arrested maturation of neutrophils[16,17].

In PEG-J feeding, copper is absorbed only *via* the upper jejunum and below, but not *via* the stomach and the duodenum. Thus, a copper intake higher than the dietary reference intake of copper is required, as shown in our patient. Copper deficiency in our patient was improved by the administration of Tezon (2 packs/d) and cocoa powder (2 spoons containing 0.7 mg of zinc and 0.38 mg of copper, per day), along with the enteral formula, *via* the jejunal feeding tube. Cocoa powder contains both zinc and copper, in a ratio of 1.8:1. It, therefore, has sufficient copper as compared to zinc. Nishiwaki *et al*[6] have also reported that copper deficiency was improved by administering 10 g of cocoa powder a day to a patient with dysphagia receiving PEG-J feed; this is consistent with our findings.

## CONCLUSION

Our findings indicate that approximately 2 mg/d of copper may be needed to prevent its deficiency. Besides the amount of copper intake, its ratio to zinc intake is also critical for maintaining adequate serum levels of copper. These findings are especially relevant in the treatment and management of patients receiving jejunal feeding. However, this study represents only one case report about copper deficiency due to jejunal feeding. As jejunal feeding is increasingly used to aid patients with difficulty in swallowing, it is critical to study the quantity of copper needed for this procedure.

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