Excess Leading to Deficiency: An Unusual Cause of Cytopenia

Jorieke Weiden,[a,*] Susan D.P.W.M. de Jonge-Peeters,[b] and Johannes M.W. van den Ouweland[a]

[a]Laboratory of Clinical Chemistry, Hematology and Immunology, Dicoon B.V., Canisius Wilhelmina Hospital, Nijmegen, the Netherlands; [b]Department of Hematology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands..

*Address correspondence to this author at: Laboratory of Clinical Chemistry, Hematology and Immunology, Dicoon B.V., Canisius Wilhelmina Hospital, C60, Postbus 9015, 6500 GS, Nijmegen, the Netherlands. E-mail j.weiden@cwz.nl.

CASE DESCRIPTION

A 49-year-old-woman presented to the hospital emergency department with complaints of severe pain in the right upper quadrant of the abdomen that had started the evening before. She experienced a continuous stabbing pain that was aggravated by deep breathing. She did not display any signs of shortness of breath, fever, nausea, or vomiting. Physical examination confirmed a localized tenderness upon abdominal palpation, with no other abnormalities noted. Initial laboratory investigations into liver function showed slightly increased alanine aminotransferase [45 U/L (reference interval [RI]: 0–35)] and alkaline phosphatase at 168 U/L (RI: 0–120) activities, whereas the other liver function tests, including gamma-glutamyltransferase, aspartate aminotransferase, and total bilirubin were within the reference intervals. Furthermore, pancreas-specific amylase activity was only slightly increased at 78 U/L (RI: 13–53). These results made it unlikely that the abdominal pain was due to acute liver disease or pancreatitis. Kidney function appeared normal, based on an estimated glomerular filtration rate of >90 mL/min/1.73 m^2 and normal urinalysis. As the abdominal pain was exacerbated by deep breathing, a D-dimer test was performed and returned a normal result [0.3 mg/L (RI: 0.0–0.5)], which excluded pulmonary embolism. A chest X-ray was performed and showed no signs of pneumonia or a pneumothorax. A serum C-reactive protein concentration was only mildly elevated at 14 mg/L (RI: 0–5 mg/L).

A complete blood count showed a severe neutropenia [0.6 $\times 10^9$/L (RI: 1.5–7.5)], lymphopenia [0.4 $\times 10^9$/L (RI: 1.0–2.8)], and a normocytic anemia [hemoglobin of 8.38 g/dL (RI: 12.09–16.11) with a mean corpuscular volume of 90 fL (RI: 80–100)]. The platelet count was near normal [403 $\times 10^9$/L (RI: 150–400)]. Microscopic analysis showed no abnormalities in leukocyte morphology. Anisocytosis was observed for the red blood cells. The cytopenias present in this patient raised suspicion for bone marrow failure. The patient was hospitalized, and a more extensive medical history was obtained. She described that prior to this recent presentation, she began having serious symptoms of fatigue, stomach complaints, and urinary incontinence. At the time, there had not been a detailed investigation by a clinician. She also had been experiencing periods of night sweats but no unwanted weight loss. For these reasons, 9 years ago, she started taking a range of supplements in consultation with an alternative medicine doctor. The patient noticed that her symptoms improved as she was using the supplements and continued supplementation based on the severity of the complaints.

CASE FOLLOW-UP

The severe hematological abnormalities observed in this patient strongly indicated a case of acquired bone marrow failure. There are various causes for acquired bone marrow failure, and as such, an extensive differential diagnosis exists (Table 1). The more frequent causes of bone marrow failure were excluded with routine laboratory testing. Her decreased red and white blood cell counts were not caused by deficiencies in iron [ferritin was 118 µg/L (RI: 10–200)], folic acid [> 45 nmol/L (RI: 7–44)], or vitamin B12 [1386 pmol/L (RI: 140–490)]. Serological testing showed that the patient did not have an ongoing

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cytomegalovirus or human immunodeficiency virus infection but did indicate IgG antibodies against Epstein-Barr virus, suggesting she had experienced an Epstein-Barr virus infection in the past. Cytopenia due to hematological malignancies, such as myelodysplastic syndrome, was considered. However, as the patient's medical history revealed that she was using supplements, further diagnostic evaluation in this direction and more comprehensive information regarding supplement use were collected.

The supplements that the patient was taking varied in types and amounts. She ingested zinc supplements on a daily basis, ranging from 0 to 75 tablets of 50 mg, which equals more than 500 times the recommended daily amount for women according to the Health Council of the Netherlands (1). She also took unspecified amounts of pyridoxal-5-phosphate (the most biologically active form of vitamin B6), magnesium, and manganese on a daily basis. In addition, she occasionally took vitamin B12, folic acid vitamin complex, copper supplements, and other supplements.

Laboratory testing of her mineral status confirmed substantially elevated levels of zinc [37.1 µmol/L (RI: 10.0–18.0)], together with undetectable low levels of copper [< 0.3 µmol/L (RI: 10.0–24.0)] and the coppertransporting protein ceruloplasmin [<0.02 g/L (RI: 0.20–0.60)]. As it was recognized that a copper deficiency induced by excessive zinc supplementation could be the cause of the patient's severe hematological abnormalities, the patient was instructed to stop taking supplements. A more detailed investigation into the cause of bone marrow failure, including a bone marrow biopsy, was considered if hematological parameters did not improve.

Discontinuation of supplementation intake led to rapid improvement of the cytopenias. Her lymphopenia was normalized within 12 days, whereas the (more extensive) neutropenia was alleviated within 33 days. Her hemoglobin concentration improved significantly within 26 days but remained slightly below the reference interval. The cytopenias improved without the need for any copper supplementation, which might have otherwise accelerated recovery. Although the patient admitted to taking small amounts of supplements again after a few weeks, her mineral status normalized over time. Her blood copper levels were back within the reference interval within 79 days, whereas her zinc levels remained elevated until 164 to 205 days after discontinuation of supplementation (Fig. 1).

QUESTIONS TO CONSIDER	
1.	What are the general causes for acquired bone marrow failure that need to be considered?
2.	Which diagnostic steps and laboratory tests are needed to determine the etiology of cytopenia?
3.	How could supplement use be related to acquired bone marrow failure?
4.	What are the potential risks of supplement use for an extended period of time, and which supplements require the most caution?

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Table 1. Differential diagnosis of acquired bone marrow failure.

Type	Potential causes
Viral infections	Cytomegalovirus
	Epstein-Barr virus
	Human immunodeficiency virus
	Parvovirus B19
	Viral hepatitis
Medications, chemicals, toxins	Chemotherapy
	Ionizing radiation therapy
	Immunosuppressive agents (azathioprine, methotrexate)
	Anti-inflammatory medication (phenylbutazone)
	Antibiotics (chloramphenicol, trimethoprim)
	Antipsychotics (e.g., clozapine)
	Blood pressure medication (e.g., nifedipine)
	Alcohol abuse
Nutrient deficiencies	Iron
	Vitamin B12
	Folic acid
	Copper
Hematological malignancies	Myelodysplastic syndrome
	Acute myeloid leukemia
	Paroxysmal nocturnal hemoglobinuria
	Large granular lymphocytic leukemia
	Multiple myeloma
	Acute lymphoblastic leukemia
Autoimmune disorders	Systemic lupus erythematosus
	Sarcoidosis
Other	Bone marrow crowding due to metastatic disease
	Hemophagocytic lymphohistiocytosis
	Idiopathic

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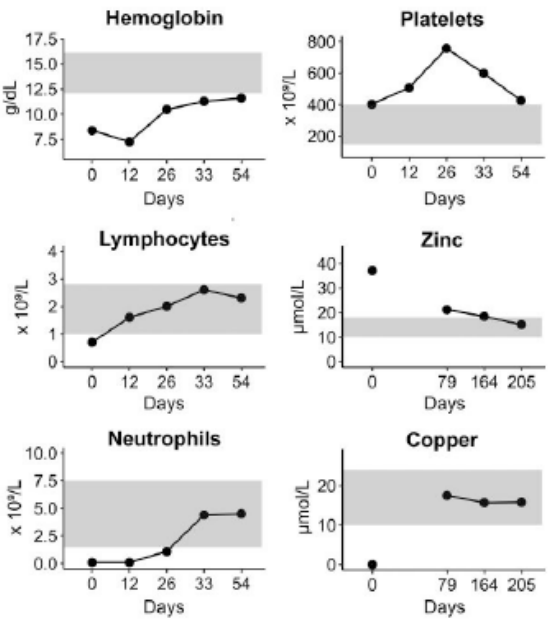

Fig. 1. Follow-up of laboratory results after discontinuation of supplementation. Grey rectangles indicate the reference intervals for each blood parameter. Days represent the number of days after discontinuation of supplementation.

REFERENCE

1. Gezondheidsraad. Voedingsnormen voor vitamines en mineralen voor volwassenen. Den Haag (the Netherlands): Gezondheidsraad; 2018.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the November 2025 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/71/11 and follow the link to the Clinical Case Study and Commentaries.

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