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When Copper Mimics Cancer: A Reversible Imposter of Myelodysplastic Syndrome

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Abstract

Copper deficiency is an uncommon but clinically significant etiology of cytopenias that can closely resemble myelodysplastic syndrome (MDS), particularly when ring sideroblasts and multilineage dysplasia are observed. This morphological overlap presents a diagnostic challenge and may lead to misclassification, unnecessary treatments, and delays in appropriate management. Here, we report the case of a 60-year-old woman who presented with progressive fatigue and was found to have severe neutropenia. Bone marrow examination demonstrated hypercellularity with marked multilineage dysplasia and ring sideroblasts, initially raising concern for MDS with sideroblastic features. Nevertheless, initially exhaustive molecular testing, including an MDS next-generation sequencing panel, SF3B1 mutation analysis, and standard myelodysplastic syndrome fluorescence in situ hybridization (MDS FISH) studies, all yielded negative findings, prompting further evaluation for other reversible causes of dysplasia. Following comprehensive laboratory studies, profound copper deficiency was revealed. The patient started receiving copper repletion, resulting in rapid hematologic recovery, sustained improvement in neutrophil counts, and near-complete resolution of dysplastic morphology on repeat marrow evaluation. The case emphasizes the importance of early consideration of nutritional deficiencies in diagnostic differentials, particularly copper deficiency, in the differential diagnosis of unexplained cytopenias and dysplasia. Early recognition is critical to avoid inappropriate initiation of disease-modifying therapy and to ensure timely, effective, and reversible management and treatment.

Keywords: ***Copper deficiency; Myelodysplastic syndrome; Sideroblasts; Cytopenias; Diagnostic pitfalls; Hematology; Nutritional deficiency.***

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1. Introduction

Copper is an important trace element required for normal hematopoiesis, iron metabolism, and mitochondrial enzymatic function [1]- [3]. Although copper deficiency is rare in the general population, its prevalence increases in individuals with malabsorptive disorders, bariatric surgery, chronic gastrointestinal disease, prior gastric bypass, prolonged proton pump inhibitor use, or excessive zinc supplementation [4]- [6]. Hematologic abnormalities associated with deficiency typically include anemia, leukopenia, neutropenia, or pancytopenia due to impaired iron mobilization and ineffective erythropoiesis [7], [8].

Bone marrow morphology in copper deficiency frequently demonstrates features that is similar to myelodysplastic syndrome (MDS), including vacuolated precursors, dysplastic hematopoiesis, and ring sideroblasts [9]-[11]. These similarities can result in significant diagnostic confusion. MDS, a clonal hematopoietic stem cell disorder, is defined by dysplastic morphology, characteristic cytogenetic abnormalities, and recurrent gene mutations such as SF3B1, TET2, and ASXL1 [12], [13]. Notably, MDS with ring sideroblasts (MDS-RS) is strongly associated with SF3B1 mutations, which occur in over 80–90% of cases [7] and [14].

In contrast, copper deficiency–related dysplasia is non-clonal and completely reversible with supplementation [15]. The presence of ring sideroblasts without an SF3B1 mutation should prompt clinicians to evaluate for nutritional etiologies [16]. Because treatment differs drastically—simple copper repletion versus chemotherapeutic or erythroid-directed therapy—accurate differentiation is essential [16].

This case report describes a profound copper deficiency mimicking MDS in clinical presentation and marrow morphology, emphasizing the importance of early nutritional evaluation in patients with unexplained cytopenias to prevent misdiagnosis and ensure appropriate treatment.

2. Case Presentation

A 60-year-old female with a history of hypothyroidism presented with severe neutropenia discovered during evaluation for fatigue and dizziness. Work-up laboratory testing revealed white blood cell count 1.2 $\times 10^9$/L, ANC (absolute neutrophil count) 0.3 $\times 10^9$/L, hemoglobin 10.2 g/dL, and normal platelet count. Peripheral smear showed neutropenia and target cells, but no blast cells.

With a concern for an underlying bone marrow disorder, the hematology oncology service performed a bone marrow biopsy. Pathology report demonstrated multilineage dysplasia, increased iron stores on Prussian blue staining, and >15% ringed sideroblasts. Blasts were estimated at 3–4% visually, but 11.7% on flow cytometry—raising concern for MDS, though this was acknowledged as potentially artifactual. The patient's MDS FISH panel, evaluating common abnormalities (−5, −7, +8, 20q−), was negative.

Genetic testing revealed no mutations in SF3B1, TET2, ASXL1, DNMT3A, or other common MDS-related genes. The absence of SF3B1 mutations, despite prominent sideroblasts, prompted clinicians to evaluate for nutritional deficiencies, including copper deficiency, as alternative causes of marrow dysplasia.

Serum copper returned at 5 mcg/dL (normal 70–175 mcg/dL) with simultaneous low ceruloplasmin. The patient began levothyroxine optimization and intravenous copper chloride infusions every four weeks (Table 1).

Table 1: Initial Labs (Lab Values).

Test	Result	Reference Range
Copper (mcg/dL)	5	70-175
WBC (x10^3/uL)	3.0	4.0-11.0
Hemoglobin (g/dL)	9.8	12.0-15.5
Platelets (x10^3/uL)	386	150-400
EPO Level (mU/mL)	<500	500-4000

After three doses, serum copper increased to 96 mcg/dL, with hemoglobin improving to 10.7 g/dL. At the three-month follow-up, copper levels rose to 134 mcg/dL. A repeat bone marrow biopsy six months after initiation of therapy demonstrated normocellular marrow with trilineage hematopoiesis and <5% ringed sideroblasts. Flow cytometry showed blasts decreased to 0.2%.

Ten months after correction, copper levels improved and remained stable at 134 mcg/dL, and cytopenias had resolved. The patient continued to experience intermittent dizziness and peripheral paresthesias attributed to diabetes-related or hypothyroidism-related neuropathy. She remained under multidisciplinary follow-up (Table 2).

Table 2: Results of the Bone Marrow Biopsy and Key Laboratory Findings.

Lab Findings	Results
Ringed sideroblast	Positive
Multilineage dysplasia	Positive

Lab Findings	Results
SF3B1, TET2, ASXL1, DNMT3A Mutation	Negative
MDS FISH panel	Negative
Copper	5 mcg/dL (low)
WBC	3.0×10^3/µL (low)
Hemoglobin	9.8 g/dL (low)
EPO	<500 mU/mL (low)

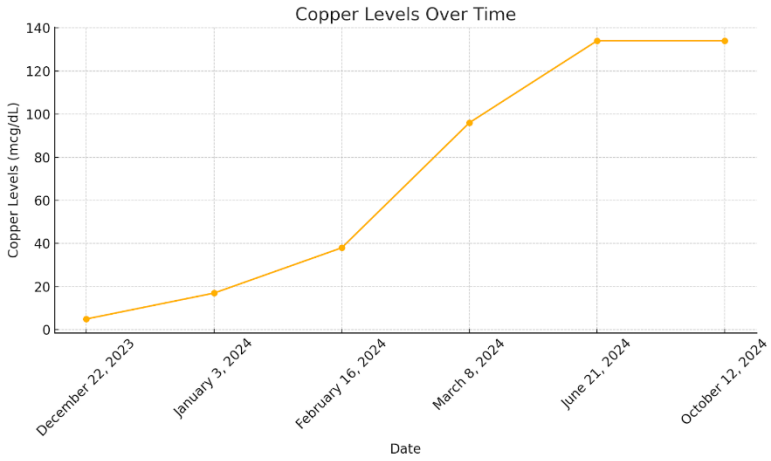

Fig. 1. Days out since initiation of IV copper chloride infusion.

3. Discussion

Copper deficiency is a reversible cause of cytopenias and dysplastic bone marrow findings, similar to those seen in MDS [1]. Copper-dependent enzymes, including ceruloplasmin, hephaestin, and cytochrome c oxidase, are integral to iron oxidation, mitochondrial function, and erythroid maturation [1], [3]. Copper deficiency impairs these enzymes, disrupting iron mobilization and resulting in mitochondrial iron accumulation and the formation of ring sideroblasts analogous to those observed in sideroblastic MDS [7], [8].

The presence or absence of mutations in genes like SF3B1, TET2, ASXL1, and DNMT3A is crucial (14, 17). The absence of SF3B1 mutations, despite sideroblasts, strongly suggests a non-clonal, nutritional etiology, guiding clinicians toward correct diagnosis and management [14], [18]. The lack of the SF3B1 mutation is particularly informative, as this gene is a defining molecular hallmark of MDS-RS and is present in most cases [14], [19]. In contrast, copper deficiency produces a phenotypically similar sideroblastic pattern but remains entirely reversible following copper supplementation [20]. Prompt hematologic improvement after copper repletion serves as both an effective diagnostic indicator and a therapeutic confirmation, distinguishing copper deficiency from clonal marrow disease [21].

This case reinforces the importance of incorporating nutritional assessments—particularly serum copper levels—early in the evaluation of unexplained cytopenias, especially when dysplastic marrow features or sideroblasts are present without supporting molecular abnormalities [22]. Because copper measurement is inexpensive and widely available, routine testing can prevent misdiagnosis and avoid unnecessary or harmful therapies, including hypomethylating agents, erythropoiesis-stimulating agents, or luspatercept [22]-[24].

4. Conclusion

Copper deficiency is a rare but reversible cause of cytopenias and bone marrow dysplasia that can closely mimic MDS. This case emphasizes the importance of early evaluation of copper levels in patients with inexplicable cytopenias, especially when patients' clonal cytogenetic or molecular markers are absent. Early identification could prevent unnecessary chemotherapy exposure and improve health outcomes by enabling complete hematologic recovery with simple supplementation.

5. Contributors

Authors are responsible for writing, editing, and patient management and will act as study guarantors. The authors approved the final version of this manuscript and are accountable for all aspects of this study.

6. Competing Interests

The author declares no competing interests.

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