Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome

Copper deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized. We report 5 patients with clinical presentation consistent with MDS who were found to be deficient in copper and whose hematologic abnormalities resolved with copper supplementation. We recommend copper level assessment in patients suspected of having low-risk MDS, especially those with gastrointestinal disorders and neuropathy.

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We wish to report on 3 patients referred to a tertiary care center over a twelve month period with anemia and bone marrow findings consistent with MDS who were found to have copper deficiency, and also two additional patients diagnosed in the past in our institution (Table 1). In our series, copper deficiency led to anemia and neutropenia in all 5 patients. Thrombocytopenia was noted in 1 patient who had undergone prior stem cell transplant. In this patient, it is unclear whether copper deficiency preceded transplantation or was secondary to malabsorption due to chronic gut graft-versus-host disease. Intravenous copper repletion was used in all patients. Correction of anemia and neutropenia in all patients indicates that copper deficiency was the underlying cause (Table 2). The myelodysplastic syndromes (MDS) represent a group of disorders characterized by anemia or other cytopenia that is often refractory to treatment. Vitamin B12 and folate deficiency are usually excluded prior to a diagnosis of MDS. Copper deficiency is not routinely considered in the work-up of these patients. However, based on our series of patients and other recent publications, we believe that evaluation for copper deficiency should be considered in select patients with bone marrow morphology otherwise consistent with MDS. The mechanism of anemia in copper deficiency may be related to the role of copper-dependent enzymes, such as ceruloplasmin and cytochrome-c oxidase, in iron metabolism and transportation.[1] Bone marrow findings of marked vacuolization of both erythroid and myeloid precursors have been consistently reported, and ring sideroblasts are also occasionally reported.[1-9] Similarly, bone marrow morphology consisted of erythroid and myeloid dysplasia in all patients, normal to increased cellularity, vacuolization of erythroid precursors, and ring sideroblasts. Cytogenetics and flow cytometry were also normal in all patients. While the actual prevalence of copper deficiency is not known, our series of patients and those reported recently by others suggests that it may be an under-recognized etiology of anemia and neutropenia appearing as MDS. Consistent with our findings of multiple patients with this diagnosis over a short time period, Huff *et al.*[1] recently reported 7 patients identified over 16 months with anemia and neutropenia who had low serum copper levels. In addition, Halfdanarson *et al.* presented a preliminary report[2] on a series of patients with copper deficiency and cytopenias in which bone marrow abnormalities including cytoplasmic vacuolization of myeloid and erythroid precursors and ring sideroblasts were noted in 10 patients. Previous reports of patients with copper deficiency and hematologic abnormalities with dysplasia have attributed copper deficiency to gastrointestinal surgery and total parenteral nutrition.[3-5] Zinc excess has also been described as an etiology of copper deficiency and associated cytopenias that typically resolved with the removal of excess zinc sources.[6,7] Other described risk factors include malabsorptive diseases, bariatric surgery, nephrotic syndrome, herbal supplements, and unusual dietary habits.[1,8,9] Consistent with described clinical risk factors, copper deficiency was thought to be related to zinc excess of unclear etiology, prior bowel resection, prior gastrectomy, and renal wast-

Table 1. Patient characteristics.

Pt	*Age*	*Sex*	*WBC (×10⁹/L) (4.5-11.0)*	*Hgb (g/L) (120-150)*	*Plt (×10⁹/L) (140-440)*	*MCV (fL) (82-96)*	*ANC (×10⁹/L) (1.9-8.3)*	*Cu (µmol/L) (12 - 23)*	*CPL (mg/L) (180 - 460)*	*Zn (µmol/L) (15-30)*	*Neuropathy*	*Marrow findings*	*Risk factors*
1	53	M	1.2	101	158	78	0.4	<1.5	< 20	30	Yes	M+E dysplasia Ring sideroblasts	Prior gastrectomy
2	32	M	0.8	77	85	91	0.24	<1.5	< 20	30	Yes	Trilineage dysplasia, Hypercellularity Ring sideroblasts	Chronic diarrhea gut, GvHD
3	39	F	1.9	52	153	91	0.8	1.9	130	NC	No	Erythroid dysplasia	Crohn's disease, Bowel surgery
4	51	F	1.4	68	147	93	0.3	<1.5	< 20	39	Yes	M + E dysplasia, Hypercellularity Erythroid vacuoles	Zinc excess of unclear etiology
5	27	M	2.6	93	257	101	0.3	<1.5	< 20	NC	No	Trilineage dysplasia, Hypercellularity Ring sideroblasts Erythroid vacuoles	Renal disorder, chronic diarrhea

Abbreviations: pt: patient number; WBC: white blood cell count; Hgb: hemoglobin; Plt: platelet count; MCV: mean corpuscular volume; ANC: absolute neutrophil count; Cu: serum copper; CPL: ceruloplasmin; Zn: serum zinc; NC: not checked; M + E: myeloid and erythroid; GvHD: graft-vs-host disease.

Table 2. Treatment and response.

Pt	Rx regimen	Time to response: Anemia	Neutropenia	Copper Level
1	Copper chloride 1.5 mg IV daily x 5 d, every other week	2 wks	2 wks	20 wks
2	Copper chloride 1 mg IV daily x 4 d	2 wks	15 wks	Uncorrected at 24 weeks
3	Copper chloride 1.75 mg IV daily x 4 d, then 1.75 mg IV weekly	4 wks	4 wks	4 wks
4	Copper sulphate 1 mg IV weekly	11 wks	11 wks	Uncorrected at 11 weeks
5	Copper chloride 3 mg IV 3x/wk	6 wks	2 wks	6 wks

ing and/or intestinal malabsorption in 4 out of 5 of our patients (Table 1). Neuropathy due to copper deficiency has also been described, with variable reversal following copper repletion.[10] In our series, neuropathy was present in 3 out of 5 patients, and symptoms reversed with copper supplementation in 1 patient.

Repletion of copper is a safe and effective means of rapidly correcting hematologic abnormalities in nearly all reported cases. Dosing of copper in patients with deficiency should be considered empiric. It should be based on hematologic response and normalization of copper levels, though the latter may not immediately follow count recovery. Oral copper supplementation may be considered, though GI intolerance may prevent this in some patients. No adverse reactions have been reported in patients receiving IV copper.

We propose that the diagnosis of copper deficiency as the etiology of anemia, neutropenia, and bone marrow dysplasia should be considered in certain patients such as young patients, those with gastrointestinal disorders, and those presenting with neurologic deficits. Evaluation of serum copper should also be considered in others who have dysplasia with normal cytogenetics and no excess blasts (i.e. low-risk MDS), as not all patients have known risk factors for copper deficiency.

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