

Copper State Among Patients Newly Diagnosed With Myelodysplastic Syndrome

Thesis

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List of abbreviations

ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AraC	Aracytabine
AST	Aspartate aminotransferase
AzaC	Azacitidine
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
COX	Cytochrome- <i>c</i> oxidase
Cp	Ceruloplasmin
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FAB	French-American-British classification
FISH	Fluorescence in situ Hybridization
HB	Haemoglobin
HIV	Human immunodeficiency virus
HSCT	Homologous stem cell transplantation
IL	Interleukin

IPSSInternational prognostic scoring system

IPSS-RRevised IPSS

JMMLJuvenile myelomonocytic leukemia

LDHLactic acid dehydrogenase

MCVMean corpuscular volume

MDSMyelodysplastic syndrome

MNCBlood mononuclear cells

MTsMetallothioneins

NCCNNational Comprehensive Cancer Network

PLTPlatelet

PNH.....Paroxysmal nocturnal haemoglobinuria

RARefractory anemia

RAEBRefractory anemia with excess blasts

RARSRefractory anemia with ringed sideroblasts

ROSReactive oxygen species

TGNThe *trans*-Golgi network

TPNTotal parenteral nutrition

WBCWhite blood cell

WHOWorld health organization

WPSSWHO prognostic scoring system

Abstract: Copper State among patients newly diagnosed with myelodysplastic syndrome

Background: Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders characterized by bone marrow failure, dysplasia, and an increased likelihood of evolution to acute myeloid leukemia (AML). Copper deficiency can be a very important treatable cause of a picture resembling MDS. A lot of cases have been reported through the years since the first case in 1994. Anemia and neutropenia caused by copper deficiency can be completely reversed by copper supplementation.

Result: Of 50 MDS patients included in the study, 4 patients were diagnosed with copper deficiency. Low serum copper correlated with anemia ($r=0.424$, $P=0.002$) and low WBCs count ($r=0.424$, $P=0.030$) and inversely strongly correlated with thrombocytopenia ($r=-0.595$, $P<0.001$). A strong statistical correlation was also found between low serum copper and ceruloplasmin level ($P=0.001$).

Conclusion: copper deficiency should be kept in mind as a treatable reversible important differential diagnosis of myelodysplastic syndrome.

Keywords: myelodysplastic syndrome, copper deficiency, differential diagnosis, anemia, neutropenia, thrombocytopenia, ceruloplasmin.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders characterized by bone marrow failure, dysplasia, and an increased likelihood of evolution to acute myeloid leukemia (AML) (**Malcovati and Nimer, 2008**).

Common examples of erythroid dysplasia include multinucleated red cell precursors, megaloblastoid maturation with nuclear-cytoplasmic developmental asynchrony, nuclear budding or internuclear bridging, karyorrhexis, ring sideroblasts, cytoplasmic vacuolization, and periodic acid- Schiff-stain positivity. Hypogranular neutrophils, hypolobated (i.e., pseudo-Pelger-Huët) neutrophils, small granulocytes, pseudo-Chediak Higashi granular inclusions, nuclear hypersegmentation, individual granulocytes containing both basophilic and eosinophilic granules (“eo-basos”), or dual esterase cytochemical staining characterize granulocyte dysplasia. Finally, megakaryocytic/platelet dysplasia is manifest as micromega-karyocytes, hypolobated or alobated megakaryocytic nuclei, as multiple widely separated nuclei, and as size and granulation abnormalities of more mature platelets (**Pfeilstöcker et al., 2005**).

Such dysplastic changes can be seen in several clinical settings: reactive conditions, due to the injurious effects of a drug or other toxin; nutritional deficiencies, such as lack of B12 or folate; or the clonal, neoplastic disorders that are collectively termed the myelodysplastic syndromes (MDS). For decades, confidently distinguishing MDS from other malignant and non-malignant entities has proven challenging (**Vardiman, 2006**).

Copper deficiency is an underrecognized cause of anemia and neutropenia. Although the morphologic features of copper deficiency in the bone marrow, such as vacuolization of early granulocyte and erythroid precursors, as well as ringed sideroblasts, have been described (**Mangles et al., 2007; Angotti et al., 2008**), the diagnosis may be difficult owing to low prevalence, a low level of clinical suspicion, and overlapping morphologic features with myelodysplastic syndromes (MDS) (**Koca et al., 2008**).

Hematologic manifestations of copper deficiency include microcytic, normocytic, and macrocytic anemia. Severe absolute neutropenia is characteristic, and thrombocytopenia occurs only in a small subset of patients (**Haddad et al., 2008**).

A diagnosis of copper deficiency is usually established by measuring serum copper or ceruloplasmin levels.