Copper State Among Patients Newly Diagnosed With Myelodysplastic Syndrome

Thesis

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By

Hebatullah Magdy Mahmoud Fares
M.B.B.CH
Faculty of Medicine Ain Shams University

Under Supervision of

Prof. Dr. Suzan Kamal Hussein
Professor of internal medicine and hematology
Faculty of Medicine Ain Shams University

Prof. Dr. Nevien Nabil Mostafa
Ass. Professor of internal medicine and hematology
Faculty of Medicine Ain Shams University

Dr. Hanaa Fathey AbdelSamee
Lecturer of internal medicine and hematology
Faculty of Medicine Ain Shams University

Faculty Of Medicine
Ain Shams University
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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-*c* 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

IPSS ..... International prognostic scoring system

IPSS-R .... Revised IPSS

JMML ..... Juvenile myelomonocytic leukemia

LDH ..... Lactic acid dehydrogenase

MCV ..... Mean corpuscular volume

MDS ..... Myelodysplastic syndrome

MNC ..... Blood mononuclear cells

MTs ..... Metallothioneins

NCCN ..... National Comprehensive Cancer Network

PLT ..... Platelet

PNH..... Paroxysmal nocturnal haemoglobinuria

RA ..... Refractory anemia

RAEB ..... Refractory anemia with excess blasts

RARS ..... Refractory anemia with ringed sideroblasts

ROS ..... Reactive oxygen species

TGN ..... The *trans*-Golgi network

TPN ..... Total parentral nutrition

WBC ..... White blood cell

WHO ..... World health organization

WPSS ..... WHO 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, thrombo-cytopenia, 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, karryorhexis, 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.