NEWS IN THE CLASSIFICATION AND THE DIAGNOSIS OF CHRONIC MYELOMONOCYTIC LEUKEMIA

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Abstract: *Chronic myelomonocytic leukemia (CMML) is a heterogeneous group of disorders with features both of myelodysplasia and of myeloproliferation,some patients showing clinical and morphologic features resembling refractory anemia with excess of blasts (RAEB) with monocytosis,and others with leukocytosis,neutrophilia,monocytosis and splenomegaly. Some common features concerning cytogenetic abnormalities, the pattern of the growth in cell cultures and clinical evolution contributes to the maintenance of this nosological entity, CMML. The intrinsic differences determined at first the separation of CMML in two forms, one named „dysplastic", more similar with RAEB and the other „proliferative", closer to chronic myeloid leukemia. The World Health Organization (WHO) classification included CMML into a new category called myelodiysplastic / myeloproliferative disorders and defined CMML I and CMML II according to medullary and peripheral blast count.*

Cuvinte cheie: *sindrom mielodisplazic, sindrom mieloproliferativ, leucemia mielo-monocitară cronică, clasificarea OMS*

Rezumat: *Leucemia mielo-monocitară cronică (LMMC) reprezintă un grup heterogen de boli cu caractere atât displazice cât şi mieloproliferative, unii pacienţi având semne clinice şi morfologice asemănătoare cu cele din anemia refractară cu exces de blaşti (AREB) cu monocitoză şi alţii, cu leucocitoză, neutrofilie, monocitoză şi splenomegalie. Unele caractere comune privind anomaliile citogenetice, modelul creşterii în culturile celulare şi evoluţia clinică au contribuit la menţinerea acestei entităţi nosologice-LMMC. Diferenţele intrinsece au determinat la început separarea LMMC în două forme, una numită „displazică", asemănătoare cu AREB şi alta „proliferativă" mai apropiată de leucemia mieloidă cronică. Clasificarea Organizaţiei Mondiale de Sănătate (OMS) a inclus LMMC într-o nouă categorie numită boli mielodisplazice / mieloproliferative şi defineşte LMMC I şi LMMC II în funcţie de numărul de blaşti din sângele periferic şi măduvă.*

INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a entity included in myelodysplastic syndrome (MDS) and is distinguished by an absolute monocytosis that exceeds 1000/µl, increased marrow myelomonocytic precursors, and single- or multilineage cytologic dysplasia.Circulating blasts should not exceed 5 %,accompanied by fewer than 20% bone marrow blasts (1).

This leukemia is part of the spectrum of clonal myeloid diseases that may have findings that simulate chronic myelogenous leukemia (CML)(2).CMML is distinguished from CML,in part,by peripheral blood monocytosis in the absence of the Ph chromosome and BCR-ABL transcript.Moreover,blood and bone marrow cells from patients with CMML show evidence of both myeloid cell dysplasia and proliferation.The World Health Organization (WHO) classification system for myeloid neoplasms designates a category „myelodysplastic / myeloproliferative diseases"(MDS/MPD), which includes myeloid disorders, such as CMML, with both dysplastic and proliferative features (3).

Classification and diagnosis

In 1976 the French-American-British Cooperative Group (FAB) introduced the term „dysmyelopoietic syndromes". Two broad types were recognized:refractory anemia with excess of blasts (RAEB) and chronic myelomonocytic leukemia (CMML), distinguishable from one other by the presence of a prominent monocytic component in the peripheral blood and bone marrow in the latter(4).In 1982 the same FAB Group proposed new criteria for the classification of myelodysplastic syndromes (MDS), defining five types:refractory anemia (RA), RA with ringed sideroblasts (RARS), RAEB, RAEB in transformation (RAEB-t) and CMML (table I)(5).

In 1994, the FAB Group proposed dividing CMML into a more myeloproliferative type (CMML-MPS) and a more myelodysplastic type (CMML –MDS) using a cutpoint of WBC of 13000/µl. A previous analysis demonstrated that this division can distinguish two clinical entities but does not provide prognostic information. Neverthelles, the IPSS group excluded CMML with a WBC of more than 12000/µl from its calculations. In a previous study, dysplastic CMML patients have been distributed to the RAEB I and II groups (6).

WHO Group (1999) creates a new diagnostic category: myelodysplastic / myeloproliferative diseases with dysplastic and proliferative features, including CMML, atypical CML (aCML), juvenile myelomonocytic leukemia (JMML) and unclassified myelodysplastic / myeloproliferative diseases (7). TheWHO added cytogenetic and/or molecular examinations to exclude bcr-abl positive CML and proposed three prognostically categories according peripheral and medullar blast counts and associated eosinophilia:CMML I with <10% medullary and <5% peripheral blasts, CMML II with 10-19% medullary and/or 5-19% peripheral blasts ,or Auer rods are present and blasts <20% in peripheral blood or bone marrow,and CMML I or

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CMML II with eosinophilia(the eosinophil count in peripheral blood >1500/µl)(8). In CMML with eosinophilia displays a rearrangement of the platelet-derived growth factor-ß receptor gene (PDGFRB) on chromosome 5q33, resulting in constitutive receptor activation (1).

In the 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia, the subgroup designated as „myelodysplastic / myeloproliferative diseases" has been renamed „myelodysplastic / myeloproliferative neoplasms" (MDS/MPN). Some cases of CMML with eosinophilia are relocated to the category „Myeloid/lymphoid neplasms with eosinophilia and PDGFRB rearrangement"(9). According to Vardiman et al.., these are„clonal myeloid neoplasms that at the time of initial presentation have some clinical, laboratory or morphologic findings that support a diagnosis of myelodysplastic syndrome (MDS), and other findings more consistent with myeloproliferative neoplasm (MPN)".These disorders comprise CMML, aCML BCR-ABL1 negative, JMML and aprovisional entity within the MDS/MPN unclassifiable group, refractory anemia with ring sideroblasts and thrombocytosis (RARS-t). The diagnostic criteria for CMML are summarized in Table II(10).

Clinical manifestations

Most patients with CMML are over 50 years of age (2).

Clinical signs and symptoms at presentation generally relate to peripheral cytopenias and are not disease specific. Many patients are asymptomatic, with a diagnosis that is established fortuitously on routine laboratory screening. Others present with fatigue, weakness, exercise intolerance, angina, dizziness as a result of unrecognized anemia, susceptibility to infection and excess bleeding.

Splenomegaly may be massive in as much as 25% of patients and, not uncommonly, is accompanied by hepatomegaly or nodular cutaneous leukemic infiltrates.Pleural and pericardial effusions and ascites may occur in CMML patients with exceedingly high or uncontrolled monocytosis. Systemic symptoms of fever and weight loss are uncommon but generally represent late manifestations of the disease or its attendant complications (1).

Laboratory data

The disease is characterized by anemia and blood monocytosis usually in excess of 1000/µl(2).

Anemia is usually normocitary, but it also can be macrocitary or with dimorphic population. The monocytes may be morphologically normal or may show atypical features such as nuclei of bizarre shapes or increased cytoplasmic basophilia or granulation (11).

The white cell count may be slightly decreased, normal, or moderately elevated. Immature granulocytes may be present in the blood, usually less than 5%.Blood myeloblasts may be absent or, when present,do not exceed 20% of total white cells. Most patients have thrombocytopenia, but normal or elevated platelet counts may occur.

The marrow is hypercellular as a result of granulo-monocytic hyperplasia; the dominant cells are early myelocytes. The proportions of myeloblasts and progranulocytes are increased but do not exceed 20% of marrow cells.Promonocytes also are increased in number. Distinction between poorly granulated myelocytes and promonocytes with primary granules can be difficult. Macronormoblasts and hyper- or hyposegmented (Pelger-Huët) neutrophils are frequent. Megakaryocytes are usually present in the marrow (2).

Discrete nodules of immature monocytic elements may be present on the trephine biopsy and can be distinguished from myeloid precursors by using a non-specific esterase stain such as alfa-naphthyl acetate esterase(1). An iron stain may show abnormal sideroblasts or increased iron stores.A myeloperoxidase (MPO) or Sudan black B (SBB) stain should be performed in all cases with an increase of blast cells, both to confirm the lineage and to exclude the presence of Auer rods (11).

Muramidase (lysozyme) activity may be increased in the blood or urine, reflecting heightened monocyte generation.

In CMML, serologic abnormalities are frequent: polyclonal gammopathy with the presence of autoantibodies, antiplatelet antibodies, erythrocyte autoantibodies and positive antiglobulin tests (1).

Biologic features

CMML is characterized by exuberant and spontaneous proliferation of granulocyte-macrophage (colony-forming unit-granulocyte-macrophage) progenitors in clonogenic assays (1).There is homozygous deletion of the genes encoding the macrophage CSF-1receptor and, also, in "spontaneous" cluster/colony growth in vitro. The latter may due to autocrine or paracrine production of growth factors such as GM-CSF and IL-3 (2).

Molecular abnormalities

Until recently, the most common known abnormality in CMML was NRAS or KRAS mutations, seen in approximately one third of cases (10). RAS proteins are involved in the transmission of growth signals from outside the cell to the nucleus; disturbances may be caused by point-mutations of the RAS genes or by altered RAS-activating proteins (4). Although recognized for many years, they remain of uncertain significance with regard to pathogenesis and prognosis. In addition, a minority of cases is positive for JAK2 (V617F).More recently, DNA array technologies have enabled the identification of novel oncogenes and tumor suppressor genes in a significant proportion of CMML: TET2, RUNX1, ASXL1 and CBL. RUNX1 and AXSL1 mutations have been founded mainly in patients with high WBC (FAB myeloproliferative variant of CMML).Patients carrying these mutant genes have aggressive or advanced forms of disease (10).

Phenotypic abnormalities

Several data analyzed by Lacronique and collaborators showed that phenotypical aberrations of the patients suffering from myelodysplasia, including CMML are CD 36 and CD117 in granulocytes and CD 56 in monocytes (12).

Prognostic features

The FAB classification enjoyed widespread acceptance because of its prognostic usefulness,to the impact of graded differences in blast percentage on leukemia transformation and cytopenic complications(1).

International Prognostic Scoring System Score (IPSS) results from data analysis from more than 800 patients with de novo MDS and nonproliferative CMML (WBC<12000/µl). This prognostic model applies a score that includes bone marrow (BM) blast percentage, cytogenetic pattern and the number of cytopenias (1).

Proliferative CMML was excluded from the IPSS model; however,a number of disease specific prognostic variables have been identified from retrospective analyses,including blast percentage as recognized by the WHO classification,white blood cell or monocyte count,anemia, thrombocytopenia,lactate dehydrogenase and spleen size.The M.D. Anderson Prognostic Score was developed as a prognostic model specific for CMML. Variables with independent prognostic significance include hemoglobin, absolute lymphocyte count, circulating immature myelomonocytic cells and BM blast percentage. These variables permit the

stratification of the patients with CMML into four prognostic categories, with a median survival from 5 to 24 months (Table III) (1).

Another score used in CMML is the Bournemouth score system modified that includes the following variables: hemoglobin<10g/dl, platelet<100000/µl, neutrophils<2500/µl or >16000/µl and blast>5%(4).

CONCLUSION

An analysis of a number of hematological and clinical parameters at diagnosis combined with information in a large series of CMML patients may help to clarify the positon of this rare disease.

Table no. 1. Diagnosis criteria for CMML according FAB (1982-1985):

1	peripheral blood and medullary monocytosis over 1000/µl
2	erythroid and/or granulocytic and/or megakaryocytic dysplasia
3	fewer than 5% blasts in the peripheral blood
4	fewer than 20% blasts in the bone marrow (initial fewer 30%)
5	absence of Auer rods in myeloid cells

Table no. 2. Diagnostic criteria for CMML according WHO (2008):

1	persistent peripheral blood monocytosis (greater than 1000/µl)
2	no Philadelphia chromosome or BCR-ABL1 fusion gene
3	no arrangement of PDGFRA or PDGFRB (particularly, in cases with eosinophilia)
4	fewer than 20% blasts in the peripheral blood and the bone marrow
5	at least one of the following: -dysplasia in one or more cell lines; -clonal cytogenetic abnormality or somatic mutation in myeloid cells; -persistence of monocytosis for at least three months with the exclusion of any other cause for this hematologic abnormality.

Subgroups:

CMML I: blasts lower than 5% in the peripheral blood, and lower than 10% in the bone marrow; •CMML II: blasts from 5% to19% in the peripheral blood, and from 10% to 19% in the bone marrow, or when Auer rods are present.

*blasts include myeloblasts, monoblasts and promonocytes, but not abnormal monocytes.

Table no. 3. Prognostic scoring system for CMML:

Risk group	Score	Number of patients(%)	Median survival (months)
Low	0 to 1	35	24
Intermediate-1	2	60	15
Intermediate-2	3	75	8
High	4	20	5

Variables (1 point each): hemoglobin<12g/dl, lymphocyte count>2500/µl, circulating immature myeloid cells and bone marrow blast>10%.

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