CHRONIC MYELOMONOCYTIC LEUKEMIA CASE PRESENTATION

CODRUȚA POPOVICI [1]

Municipal Hospital of Cisnădie

Keywords: *myelodysplastic syndrome, myeloproliferative syndrome, chronic myelomonocytic leukemia, monocytosis*

Abstract: *Chronic myelomonocytic leukemia (CMML) is a heterogeneous group of disorders with features both of myelodysplasia and of myeloproliferation: myelodysplastic / myeloproliferative diseases. In the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, the subgroup designated as „myelodysplastic / myeloproliferative diseases" has been renamed „myelodysplastic / myeloproliferative neoplasms (MDS/MPN). This subgroup comprises CMML, atypical chronic myelogenous leukemia (aCML) juvenile myelomonocytic leukemia (JMML) and a provisional entity within the MDS/MPN unclassifiable group, refractory anemia with ring sideroblasts and thrombocytosis (RARS-t). I present the case of a 76 years-old male admitted in Hematology Department of Sibiu County Hospital for the analysis of the leukocytosis with splenomegaly. The clinical exam and the paraclinic investigations of this patient were performed: the hemogram with cytology, morphological and hystopathological exam of bone marrow, cytogenetic study and molecular biology tests. The patient presented in Hematology Department in may 2007 with splenomegaly. The hemogram showed leukocytosis (90000/µl) with deviation to the left of the leucocyte formula to 2% myeloblasts and monocytosis (1800/µl). The bone marrow aspirate and biopsy showed hipercellularity with trilineal myelodysplasia. The cytogenetic study revealed the absence of Philadelphia chromosome. The molecular biology tests were negative for BCR-ABL1. The patient presents criteria of CMML I (WHO criteria). The patient followed treatment with Hydreea. The presence of this rare disease, chronic myelomonocytic leukemia, underlines the importance of performing complete paraclinic investigations for elucidation of this entity.*

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

Rezumat: *Leucemia mielo-monocitară cronică (LMMC) reprezintă un grup heterogen de boli cu caractere atât mielodisplazice cât şi mieloproliferative: boli mielodisplazice / mieloproliferative. După revizuirea clasificării Organizației Mondiale de Sănătate (OMS) a neoplasmelor mieloide şi a leucemiei acute (2008), subgrupul „boli mielodisplazice/mieloproliferative" a fost renumit „neoplasme mielodisplazice/mieloproliferative". Acest subgrup include LMMC, leucemia mieloidă cronică atipică (LMCa), leucemia mielo-monocitară juvenilă (LMMJ) şi o entitate provizorie din grupul neoplasmelor mielodisplazice/mieloproliferative neclasificabile, anemia refractară cu sideroblaşti inelari şi trombocitoză (ARSI-t). Prezint cazul unui pacient în vârstă de 76 ani internat în Secția de Hematologie a Spitalului Clinic Județean Sibiu pentru leucocitoză cu splenomegalie. Acestui pacient i-au fost făcute examenul clinic şi următoarele investigații paraclinice: hemograma cu examenul citologic,examenul morfologic şi histopatologic al măduvei osoase, studiul citogenetic şi testele de biologie moleculară. Pacientul s-a internat în Secția de Hematologie în mai 2007 pentru splenomegalie. Hemograma a arătat leucocitoză (90000/µl) cu deviere a formulei leucocitare la stânga până la 2% mieloblaşti şi monocitoză (1800/µl). Aspiratul şi biopsia măduvei osoase au evidențiat hipercelularitate cu mielodisplazie triliniară. Studiul citogenetic a indicat absența cromozomului Philadelphia. Testele de biologie moleculară au fost negative pentru BCR-ABL1. Pacientul prezintă criteriile LMMC I (criteriile WHO).Pacientul a urmat tratament cu Hydreea. : Prezența acestei boli rare, leucemia mielo-monocitară cronică, subliniază importanța efectuării investigațiilor paraclinice complete pentru elucidarea acestei entități.*

INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a controversed pathogenic entity with features both of myelodysplasia and of myeloproliferation. Diagnostic criteria in CMML are absolute monocytosis that overpasses 1000/µl, citopenia, trilineal myelodysplasia and myeloproliferation associated with hepatosplenomegaly, leukocytosis, increased number of granulo-monocitare colonies (CFU-GM) in bone marrow (1).

The World Health Organization (WHO) classification from 1999 included CMML into a new diagnostic category called myelodysplastic/myeloproliferative disorders (2).The WHO added cytogenetic (Philadelphia chromosome) and/or molecular examinations (BCR-ABL1 fusion gene) to exclude BCR-ABL1 positive chronic myelogenous leukemia (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

[1]Corresponding Author : Codruța Popovici,14. Nicolae Beldiceanu street, Sibiu, România; e-mail: tatucodruta@yahoo.com; tel +40-0269226248
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marrow,and CMML I or CMML II with eosinophilia (the eosinophil count in peripheral blood >1500/µl)(3).

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). These disorders comprise CMML,atypical CML, juvenile myelomonocytic leukemia (JMML) and a provisional entity within MDS/MPN unclassifiable group,refractory anemia with ring sideroblasts and thrombocytosis (RARS-t).Some cases of CMML with eosinophilia are relocated to the category „Myeloid/lymphoid neoplasms with eosinophilia and PDGFRB rearrangement ” (4).

I present the case of a patient diagnosed in Hematology Department of Sibiu County Hospital with LMMC I.

RESULTS AND DISCUSSIONS

A 76 years old patient presented in May 7, 2007 an accidental head injury in the coccyx and is admitted to surgery at which time it reveals leukocytosis and splenomegaly.

Haematological advice is required,raising the suspicion of CML laboratory,but the patient does not meet the citeria for CML chronic phase,outlined the picture of a rather CMML, peripheral monocytosis being 18000/µl.The patient presented leukocytosis (90000/µl) with deviation to the left of the leukocyte formula to 2% myeloblasts,basophils 1%, monocytosis 20%,platelets 100000/µl,FAL 26.

Bone marrow aspiration reveals aspect of myelodysplastic syndrome, CMML, but can not exclude an atypical CML, reason for requesting the bone marrow histopathology and cytogenetic and/or molecular examinations.

Abdominal ultrasound shows inhomogeneous liver, 18 cm,busy gallbladder stones, portal vein to limit,spleen 20 cm,accessory spleen in hil 2 cm,diverticular bladder with polycyclic shape. Paraclinical hospitalization in surgery mentiones the leukocytes number (WBC) 89600/µl, hemoglobin(Hb) 10,6g/dl, hematocrit(Ht) 32,5%, platelets 100000/µl.

Peripheral blood analysis in Hematology Department showed : WBC 49100-23300- 19600-13100/µl;Hb 9,8-9,4-9,7-9,2 g/dl;Ht 31-30,3-30,2-29%;platelets 83000-58000-60000-43000/µl;leukocyte formula:blasts 2%,myelocytes 3%, metamyelocytes 8%,bands 8%, polymorphonuclear neutrophil (S) 48%, basophils (B)<1%, lymphocytes 10%, monocytes 20%; erythroblasts 2/100 leukocytes; erythrocyte morphology: moderate anisocytosis (microcytes,rare polychromatophilic macrocytes), moderate poikilocytosis (erythrocytes in the drops, ovalocytes, rare microspherocytes), light/moderate hypochromia; presence of hypogranular and hyposegmented neutrophils; platelets arranged in groups of 6 with platelet anisocytosis (figures 1 and 2). Table no. 1. shows the evolution of the blood counts.

Microscopic examination of the bone marrow (BM) shows hipercellularity,the dominant cells represented in the majority of granulocyte series,some with dysplastic changes hypo / agranular, rare with circular nucleus or with asynchrony. Percentage of blast cells ≈5%, basophils≈1%, increased monocyte - macrophage series: monocytes≈20% (by morphological aspect, cytochemical confirmation≈12%). Megakaryocyte series: rare megakaryocytes with normal morphological aspect, frequently micromegakaryocytes, groups of normal platelets with moderate anisocytosis, rare erythroblasts(1-2%) some with dysplastic aspect (abnormal nuclear shape,basophilic stippling). Small lymphocytes≈10%. Conclusion: hyperplastic BM with aspect of myelodysplastic / myeloproliferative syndrome-CMML or atypical CML.An iron stain shows presence of iron stores in macrophages, sideroblasts 30%,FAL 26, a non-specific esterase stain (Leucoguost EST) reveals in the BM smears an intense positive reaction in 12% of elements (figure 3).

Figure no. 1. Chronic myelomonocytic leukemia-peripheral blood smear coloured May-Grünwald-Giemsa. The observation shows dysplastic modifications in granulocytic line (hypogranular neutrophil) and erythroid line (poikilocytosis).

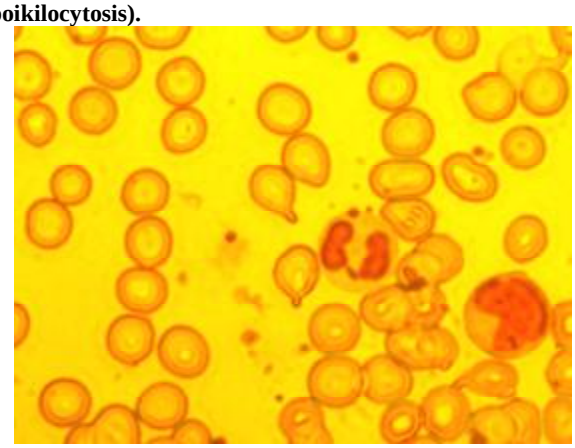

Figure no. 2.Chronic myelomonocytic leukemia-peripheral blood smear coloured May-Grünwald-Giemsa. The observation shows hyposegmented neutrophil (pseudoPelger-Huët), dysplastic modifications in platelet line (anisocytosis) and a monocyte.

Figure no. 3.Chronic myelomonocytic leukemia-bone marrow smear coloured Leucoguost EST with positive reaction in monocytes

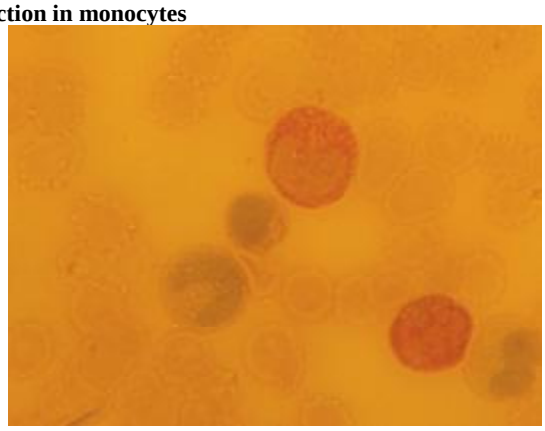

Table no. 1. Evolution of the blood counts in time.

Parameter	Values (number/µl)								
	7.o5. 2007	12.06.2007	15.08.2007	7.09.2007	15.10.2007	16.11.2007	28.01.2008	26.08.2008	30.10.2008
Leukocytes	89600	83500	9700	24800	39100	12350	6100	104000	234000
Monocytes	18000	29225	2037	6448	6256	3952	1708	32240	70200

Histopathology examination of the BM shows BM with cellularity 90% due to proliferation of granulocyte series elements with blasts less than 15% and increased granulocyte precursors; the monocytic population can not be distinguished;the erythroid population:isolated precursors elements with dysplastic aspects and reduced maturation; frequently megakaryocytes in large clusters with presence of dysplastic and hyperlobulated elements; present reticulin fibrosis and focal collagen fibrosis; absent marrow iron stores.Histopathological diagnostic:aspect of chronic myeloproliferative disease-CML.

Cytogenetic study was not observed the presence of Philadelphia chromosome. Molecular biology tests were negative for BCR-ABL1.

Clinical data and laboratory investigations sustain myelodysplastic/myeloproliferative syndrome diagnosis-CMML (5).Diagnosis is based on the next elements:

- clinical examination:splenomegaly;
- persistent peripheral blood monocytosis (greater than 1000/µl);
- absence of Philadelphia chromosome and of BCR-ABL1 fusion gene;
- fewer than 20% blasts in the peripheral blood and the bone marrow;
- dysplasia in erythroid,granulocytic and megakaryocytic lines.

The patient presents criteria of CMML I (WHO criteria)-blasts 2% in the peripheral blood and 5% in the bone marrow (6).It was initiated the treatment with Hydreea 3 tablets/day, Milurit 300 mg 3tablets/day below which the number of leukocytes reached after fifteen days of hospitalization 13000/µl and spleen decreased significantly (spleen 4 cm under the rib board).

CMML is a disease with features both of myelodysplasia and of myeloproliferation. First CMML was included in myelodysplastic syndromes (1982) (7), but the controversy begins due to mieloproliferation aspect with relationship with CML (8).In the case described, the differential diagnosis of CMML with CML is revealed by peripheral monocytosis with absence of Philadelphia chromosome and of BCR-ABL1 fusion gene. Moreover, blood and bone marrow cells from patient show evidence of both myeloid cells dysplasia and proliferation (9).

CMML needs to be distinguished from aCML with which it shares some features.It has been recommended that cases in which more than 15% of circulating white cells are granulocyte precursors (promyelocytes, myelocytes and metamyelocytes) and monocytes lower than 10% of circulating leukocytes (5) should be categorized as aCML and cases with fewer than 15% granulocyte precursors as CMML (10).

CONCLUSIONS

Presence of this rare disease underlines the importance of complete paraclinic investigations for correct diagnosis of this entity.

Therapy with Hydreea is limited and it becomes necessary to develop other treatment modalities, although CMML remains a disease with unfavourable prognosis and unforeseeable evolution.

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