THE SYNDROME OF ABNORMAL CHROMATIN CLUMPING - CASE REPORT

GABRIELA ARIADNA GAVRILĂ[1], LIVIA DRĂGHILĂ[2], CRISTINA BUȘ[3]

[1,2,3]*Emergency County Hospital Sibiu,*[1] *"Lucian Blaga" University of Sibiu*

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Abstract: *The syndrome of abnormal chromatin clumping is a rare morphological entity consisting of an exaggerated clumping of nuclear leukocytes chromatin. We report the case of an 81 year-old man admitted for persistent anemia-related symptoms. Complete blood count reveals low hemoglobin, low number of platelet, normal number of white blood, leukoerythroblastic picture, hypercellular bone marrow with abnormal chromatin clumping in myeloid series cells, small megakaryocytes, with non-lobulated nucleus. Readmitted after 7 months, the patient presents leukocytosis with differential deviated to left up, without basophilia or monocytosis, hypercellular bone marrow, increased granulocytic series with abnormal chromatin condensation, small megakaryocytes with non-lobulated nucleous. BCR-ABL translocation were negative. The diagnosis has been established to abnormal chromatin clumping syndrome. Thereafter, the patient had an unexpected evolution. Initially classified as myelodysplastic syndrome, it has acquired a granulocytes proliferative character. So, it was reconsidered as a myelodysplastic/myeloproliferative neoplasm. Morphology remains fundamental at the beginning of the diagnostic algorithm for dysplasia.*

INTRODUCTION

The syndrome of abnormal chromatin clumping is a rare distinct morphological entity consisting of an extremely exaggerated clumping of nuclear chromatin in leukocytes, mimicking nuclear fragmentation. Nuclear chromatin clumping is often associated with a loss of segmentation in the neutrophils.

Since the first case reported by Gustke, et al. (1) this entity was difficult to classify into the malignant haematological diseases system. Probably due to many similarities in clinical and biological behaviour with chronic myelomonocytic leukemia, it has been framed among myelodysplastic syndromes (MDS).(2) A number of authors categorize it like a myelodysplastic syndrome with elements of myeloproliferative syndrome. Other authors categorize it as atypical chronic myeloid leukemia or Ph-negative chronic myeloid leukemia (CML).

According to the 2008 revision of World Health Organization (WHO) classification of acute leukemia and myeloid neoplasms, this entity is a variant of aCML BCR-ABL1 negative, included in myelodysplastic/myeloproliferative neoplasms (MDS/MPN). The MDS/MPN are characterized by concomitant myelodysplastic and myeloproliferative features. This category includes besides aCML, chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), MDS/MPN-unclassifiable (MDS/MPN-U) and starting with WHO 2016 MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), recognized as a distinct entity.

Most cases reported as variant of aCML BCR-ABL1 negative are characterized both in the peripheral blood and bone marrow by an increased number of neutrophils and precursors with exaggerated condensation of the nuclear chromatin. The predominant aspect of aCML is pronounced dysgranulopoesis. It can be observed also acquired Pelger-Huet or other nuclear abnormalities, clumped nuclear chromatin, bizarrely segmented nuclei or even abnormal cytoplasmic granularity.

CASE REPORT

We report the case of an 81 year-old man patient, PI, from Sibiu, with a history of hypertension, tip 2 diabetes, stroke, chronic ischaemic heart disease, thyroidctomy, gout, acute gangrenous cholecystitis with cholecystectomy, epilepsy, chronic obliterative arteriopathy of the inferior limbs, three episodes of Clostridium difficile colitis. He was admitted in May 2017 to our hospital for persistent anemia-related symptoms. His physical examination shows pale skin and mucous. Complete blood count reveals a hemoglobin of 8.8 g/dL, MCV 112.1 fL, platelet count 32.000 /µL, white blood cell (WBC) count 8.350 /µL with a WBC differential showing the presence of immature cells of the myeloid series and nucleated red cells in the circulating blood (leukoerythroblastic picture). Blood levels of iron, ferritin, glucose, transaminases were normal. Bone marrow was hypercellular, with abnormal chromatin clumping in granulocytes and myeloid precursors and neutrophil whose nucleus is hyposegmented. More of the megakaryocytes were small, with non-lobulated nucleus which raises the suspicion of myelodysplastic syndromes with a deletion *5q*. Cytogenetic analysis does not confirm 5q deletion. So, the diagnostic remain refractory cytopenia with multilineage dysplasia and the patient received erythropoietin therapy for his anemia.

In December 2017, the patient returns to our hospital in a good general condition, no special subjective symptoms, discreet pale skin. Biological status reveals: partially corrected anemia, leukocytosis 79.290/µL (figure no.2), a shift to the left in the differential count up to myeloblast, without basophilia or monocytosis, elevated LDH, slightly increased uric acid. This time bone marrow was also hypercellular, with increased granulocytic series, marked disgranulopoiesis, numerous

[1]Corresponding author: Gabriela Ariadna Gavrila, B-dul. Coposu, Nr. 2-4, Sibiu, România, E-mail: gcocisiuu@yahoo.com, Phone: +40766 449285
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neutrophil granulocytes with a pseudo-pelger nucleus and abnormal chromatin condensation, without blasts excess (1-2%) small megakaryocytes with non-lobulated nucleous. Molecular testing for BCR-ABL translocation were negative. The diagnosis has been established to abnormal chromatin clumping syndrome (variant of atypical chronic myeloid leukemia BCR-ABL1 negative) and followed a treatment with Cytosar and Hydreea with good clinical evolution but with increasing white blood cells levels. During admission he developed acute Candida pneumonia with progressive respiratory failure, acute pulmonary edema and finally, the patient had died despite treatment applied.

Figure no.1. White blood cell changes in peripheral blood and bone marrow aspirate (Wright-Giemsa stained, 100x)

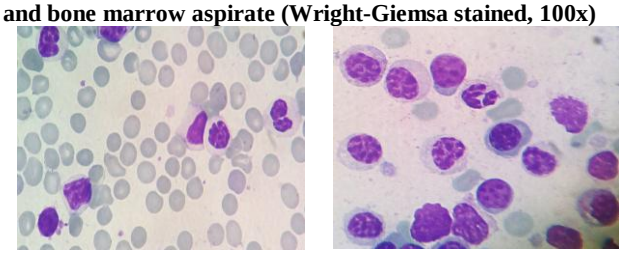


Figure no. 2. Evolution of WBC count

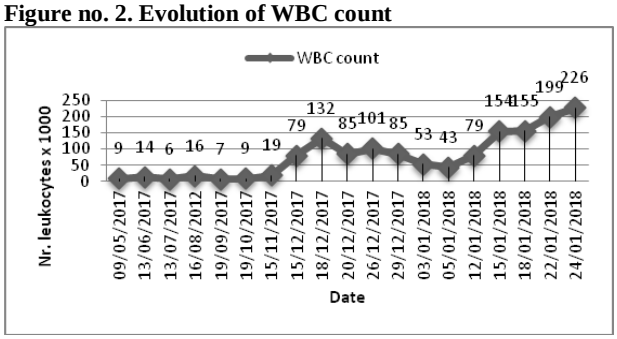


Figure no. 3. Evolution of haemoglobin

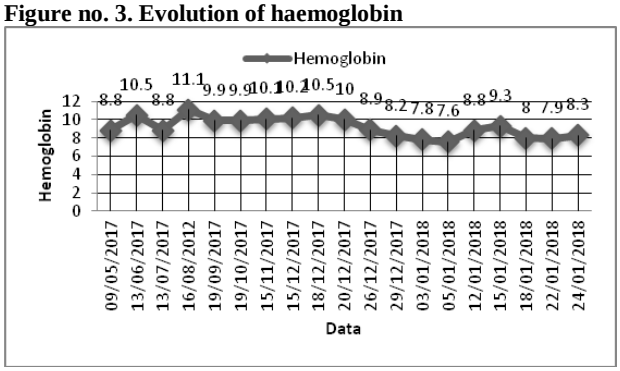
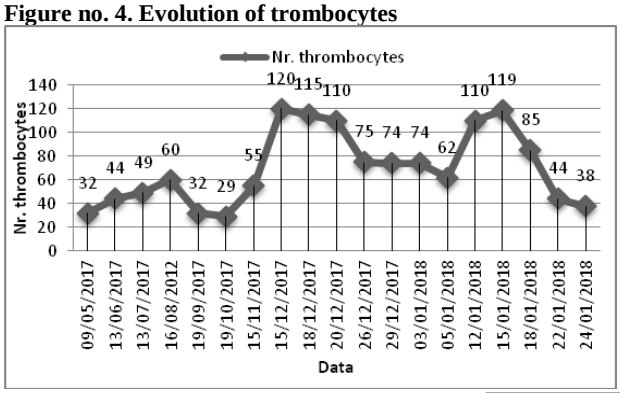


Figure no. 4. Evolution of trombocytes

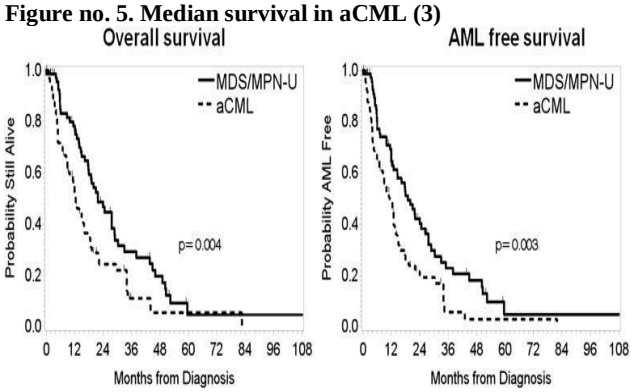


DISCUSSIONS

The patient had an unexpected evolution within 7 months of first admission. Initially he presented bicitopenia (anemia and thrombocytopenia), hypercellular bone marrow, significant dysplasia involving at least two myeloid hematopoiesis cell lineages (granulocytic, megakaryocytic) leading to a myelodysplastic syndrome diagnostic. Thereafter, it has acquired a granulocytes proliferative character, maintaining and accentuating the abnormal appearance of chromatin condensations, without responding to cytoreductive treatment. Therefore, it was more appropriate to classify as a myelodysplastic/myeloproliferative neoplasms, namely aCML.

Atypical chronic myeloid leukemia is a clonal disorder, a rare subtype of myelodysplastic/myeloproliferative (MDS/MPN) syndromes group with poor prognosis.The median survival is about 24 month with standard therapy.

Figure no. 5. Median survival in aCML (3)



MDS/MPN overlapping myelodysplastic bone marrow failures of myelodysplastic syndromes and myeloproliferative changes of myeloproliferative neoplasms.

The karyotype of patient with MDS/MPN is generally normal but we can find abnormalities shows in MDS.(4) Using of next-generation sequencing is opening the way to discover the gene mutations that corresponds to clinical features.

Table no. 1. Recurrent cytogenetic abnormalities in MDS (5)

Chromosomal abnormality	Key genes deleted	IPSS-R risk category	Clinical features
Normal	--	Good	
del(5q)	CSNK1A1, RPS14, EGR1, APC, DDX41, HSPA9, miR-145, miR-146a	Good	Sensitive to lenalidomide.
Monosomy 7 or del(7q)	EZH2, MLL3, CUX1	Poor	Monosomy 7 may have a worse prognosis than del(7q).
Trisomy 8	Unknown	Intermediate	High response rate to immunosuppression
Trisomy 19	Unknown	Intermediate	
del(20q)	MYBL2, TP53RK, TP53TG5	Good	Often associated with mutations in splicing factors
del(17p)	TP53	N/A	Poor response to alloHSCT
Complex[1] and monosomal	TP53	Poor to very poor	Associated with ***TP53*** mutation
del(11q)	MLL, ATM	Very good	
"-Y"	Unknown	Very good	May not be pathogenic, but instead may be lost during normal aging.

IPSS-R- Revised International Prognostic Scoring System.

Atypical chronic myeloid leukemia resembles classical chronic myeloid leukemia, but missing BCR-ABL1

gene rearrangement and specific MPN mutations (JAK2, MPL, CALR). Therefore, tyrosine kinase inhibitors very potent, selective and successful treatment for CML are inadequate in aCML.

Update 2016 aCML diagnosis requires the following criteria:

Table no. 2. aCML diagnostic criteria (4)

Peripheral blood leukocytosis due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes, metamyelocytes) comprising ≥10% of leukocytes)
Dysgranulopoiesis, which may include abnormal chromatin clumping
No or minimal absolute basophilia; basophils usually <2% of leukocytes
No or minimal absolute monocytosis; monocytes <10% of leukocytes
Hypercellular bone marrow with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
<20% blasts in the blood and bone marrow
No evidence of PDGFRA, PDGFRB, or FGFR1 rearrangement, or PCM1-JAK2
Not meeting WHO criteria for BCR-ABL1+ CML, PMF, PV, or ET*

* PMF- Primary myelofibrosis, PV- Polycythemia vera, ET- Essential thrombocythemia.

Atypical chronic myeloid leukemia may be more difficult to differentiate from chronic myeloid leukemia which usually has neutrophilia with no dysplastic granulocytes, prominent basophils, no thrombocytopenia, no anemia and BCR-ABL present.

The leukemoid reactions must be differentiated through WBC counts, lower than 50×10^9/L, toxic granulocytic vacuolation, Döhle's bodies in the granulocytes and generally suggestive clinical history and physical examination for the origin of the leukemoid reaction.

Molecular basis of aCML is poorly understood. Identifying mutations are:

- somatic SETBP1 mutations in 25% of aCML cases. The SETBP1 mutants (encoding a p.Gly870Ser alteration) exhibited higher levels of SET protein, lower phosphatase 2A activity and higher cellular proliferation. These findings suggest SETBP1 mutations is a newly discovered oncogene involved in the development of aCML.(6) SETBP1 mutations in aCML are associated with higher white blood cell counts at diagnosis and poorer survival;(7)
- the activating mutations of the colony-stimulating factor 3 receptor, CSF3R, in 40% of the aCML patients;(8)
- somatic mutation CSF3R and SETBP1 can coexist in 5% of cases;(8)
- ETNK1 in 9% of atypical chronic myeloid leukemias, is associated with the impaired catalytic activity of ethanolamine kinase;(9)

Recurrent mutations in CSF3R and SETBP1 genes are able to conferring a proliferative advantage to mutated cells;(7)

CONCLUSIONS

Despite the "blue book" WHO 2016 Classification of Tumours of Haematopoietic and Lymphoid based on multiparameter approach to define diseases, morphology remains and will continue to be the first step of the diagnostic algorithm and classification for dysplasia. Gene expression profile and analysis of point mutations should be integrated in the future with morphology and cytogenetics findings, especially in patients with normal karyotype.

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