Therapeutics, Pharmacology and Clinical Toxicology
Vol XVIII, Number 2, June 2014
Pages: 72-77

THERAPEUTICAL PRACTICE

ASSESSMENT OF PROGNOSTIC FACTORS IN MYELODYSPLASTIC SYNDROMES

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Abstract. Myelodysplastic syndromes (MDSs) represent a heterogeneous group of bone marrow conditions characterized by peripheral blood cytopenias and increased risk for evolution to acute leukemia. An accurate risk group classification constitutes the start point for the establishment of the therapeutic attitude in MDS pathology. The prognostic relies on different risk models, some of them being disease related: French-American-British system (FAB), World Health Organization classification, International Prognostic Scoring System (IPSS), WHO Prognostic Scoring System (WPSS), MD Anderson Scoring System (MDACC), while others being patient and comorbidities related: MDS- specific Comorbidity Index (MDS-CI). In 2012, Peter L. Greenberg and collaborators published in Blood the Revised International Scoring System (R-IPSS) that included MDS patients in five risk groups, based on cytogenetic changes. The evolution of patients with low risk MDS is heterogeneous and in most cases influenced by an associated pathology, considering that myelodysplasia occurs more frequently in elder people. By correlating the data in literature, a risk group classification was applied in the case of a 65 years old male patient, based on several of the above mentioned models. The patient was diagnosed with MDS in 2009 - refractory cytopenia with multilineage dysplasia and ringed sideroblasts (WHO 2008) in the Haematology Clinic of "Colentina" Hospital, Bucharest. At admission the patient presented a normal karyotype and he was classified in Intermediate 1 risk group (IPSS Int-1); Intermediate risk (WPSS); Low risk (MDACC); Low risk (MDS-CI). Our patient soon became transfusion dependent, with a requirement of 3 units of packed red blood cells per month and repeated hospital admissions. He also developed progressive left-ventricular dysfunction secondary to severe anaemia and recurrent transfusions. After approximately four years, in May 2013, the patient's reclassification based on risk models indicated an intermediate risk (WPSS), the same as that at the moment of the diagnosis, but the associated comorbidities (transfusion dependency and heart failure) shifted him to a higher risk group, according MDS Co-morbidities Index (MDS-CI Int-High Risk), with low chances of survival, confirmed by his death shortly after, due to staphylococcal endocarditis but no leukemic transformation. Considering these events it becomes clearer that for MDS patients staged in low and intermediate risk groups, comorbidities represent an independent risk factor which entails a reassessment of the current prognostic systems.
Keywords: Myelodysplastic syndromes (MDS), risk models, WHO, IPSS, WPSS, MDACC, MDS-CI, R-IPSS prognostic scoring systems

Introduction

Myelodysplastic syndromes (MDSs) are a heterogeneous group of stem cell clonal disorders characterised by ineffective hematopoiesis and predilection for acute leukaemia (AL) transformation. The diagnosis is set based on the patient's history and the changes in the peripheral blood; it requires cytological +/- immunohistochemistry examination of the peripheral blood and bone marrow which is the essential part of the diagnosis [1]. Cytogenetic and molecular examinations contribute to the understanding of the pathogenic mechanisms and to the risk group staging. Prognostic factors and staging into risk group of transformation to AL are elements under permanent change. Therapeutic strategy in myelodysplastic syndromes depends on the risk group staging. By bringing on the same page the data in the literature, it is recommendable to elaborate a "risk model" for evolution into AL or death, that focuses on the predictability degree of certain parameters such as: World Health Organization classification, degree of cytopenias, serum ferritin level and transfusion requirement, percentage of blasts, myelofibrosis, as well as cytogenetic and molecular abnormalities [2,3,4,5].

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Diagnosis and risk group staging

Myelodysplastic syndromes constitute a heterogeneous group of conditions that are difficult to diagnose, often underdiagnosed or misdiagnosed or caught in the transition phase to AL. In the case of an MDS suspicion the primary objective is to establish correctly the diagnosis and the risk group staging.

An analysis of recently presented data during the 4th International Conference on Myleodysplastic Syndromes (Estoril, Portugal, 15-17 May 2014) revealed an establishment of the main diagnostic and staging in the risk group criteria, that prove to be real challenges to the medical community. Professor Luca Malcovati (Pavia) presented new data on the risk factors analysis, emphasising the impact of the new revised IPSS risk model (Revised - International Prognostic Scoring System) on the clinical practice.

The "Genetics and epigenetics of MDS" session constituted an opening for the discussions and papers presented at the 19th Congress of the European Haematology Association (Milan, 12-15 June 2014). Thus, mutations and deletions identified in MDS patients have been classified as follows: epigenetic modifications (including TET2 and DNMT3A), RNA alterations ("RNA splicing", including SF3B1 and U2AF1) and translocation involved in protein synthesis, including RPS14. For patients with MDS, applying these molecular investigations in the clinical practice will improve the diagnosis, risk group classification, prognostic estimates, as well as the treatment response prediction.

In myelodysplastic syndromes (MDS), a proper risk group staging constitutes the basis for the future therapeutic attitude. The review of the prognostic models in the literature highlights that prognostic in MDS patients relies upon different risk models, some being disease related: French-American-British system (FAB), World Health Organization classification, International Prognostic Scoring System (IPSS), WHO Prognostic Scoring System (WPSS), MD Anderson Scoring System (MDACC), while others being patient and comorbidities related: MDS-specific Comorbidity Index (MDS-CI) [6,7,8,9]. FAB and WHO classifications do not take into consideration the cytogenetic modifications. The International Prognostic Scoring System (IPSS) is the instrument the most frequently used for staging of MDS cases at the moment of diagnosis, but it underestimates the role of transfusion dependency and of cytogenetic markers. The WHO Prognostic Scoring System (WPSS) can be used throughout the disease evolution but it fails to take into account chromosomal modifications. Finally, the MD Anderson Cancer Center (MDACC) system can be applied in secondary MDSs, while MDS Comorbidities Index (MDS-CI) system assesses the role of co-morbidities. In 2012, Peter L. Greenberg and collaborators published in Blood a material on The Revised International Scoring System (R-IPSS) that included MDS patients in five risk groups, based on cytogenetic changes [10]. In an effort to estimate the global survival rate and time to AL evolution, the authors' group, led by Maria Teresa Voso validated the R-IPSS system as a significant predictor. [11]

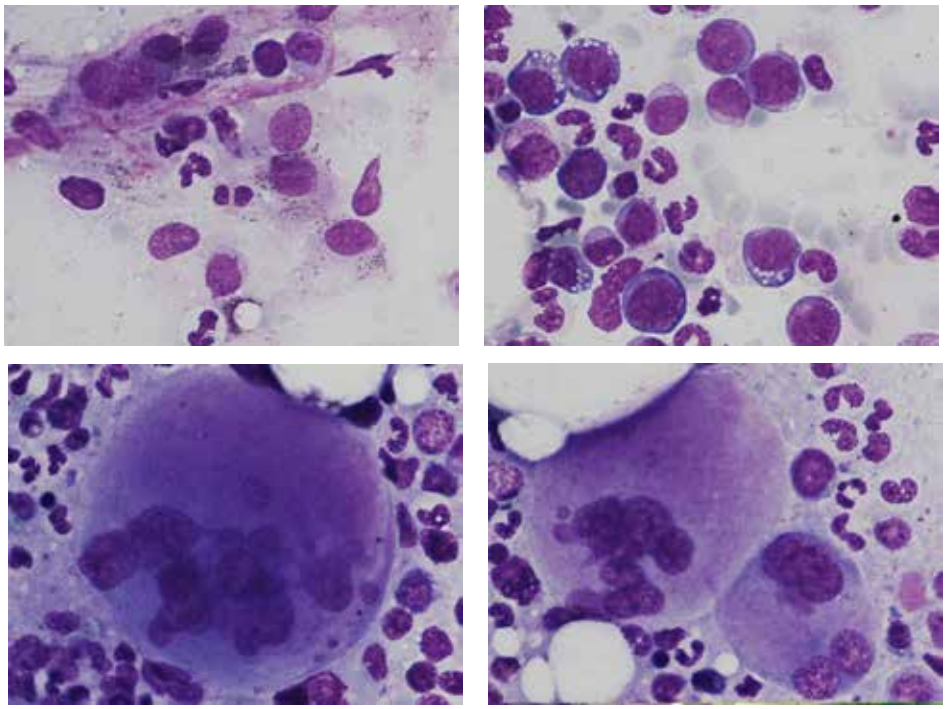


Figure 1. November 2009, May-Grünwald Giemsa stain, bone marrow aspirate: hypercellularity (80%), dyserythropoiesis, dysgranulopoiesis, giant megakariocytes

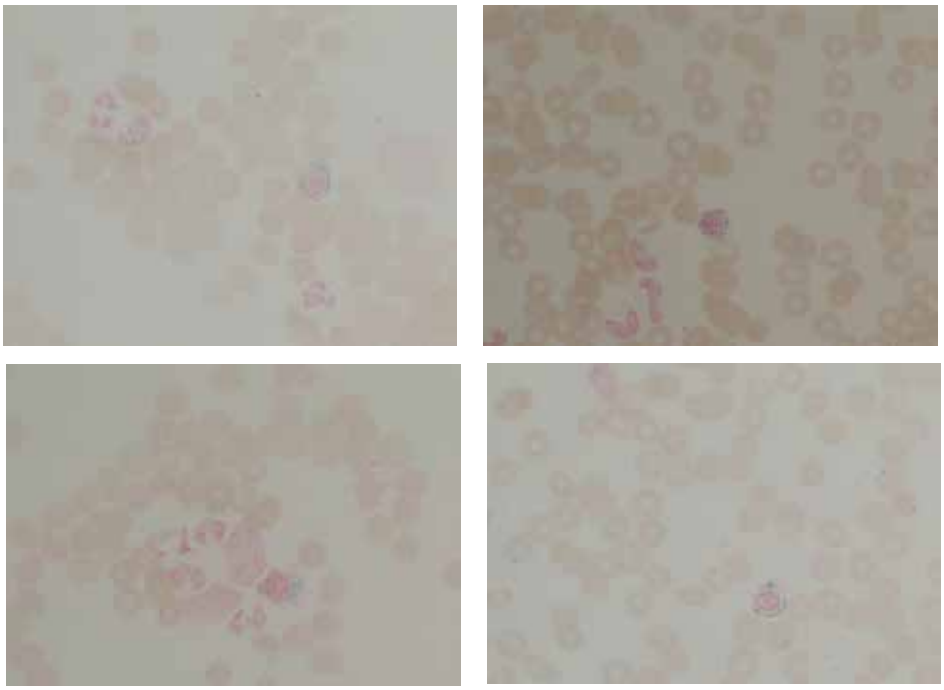


Figure 2. November 2009, Pearls stain, bone marrow aspirate: 20% ringed sideroblasts

Material and methods

By bringing together data in literature, a risk group classification was applied in the case of a 65 years old male patient, based on several of the above mentioned models. The patient was diagnosed with MDS in 2009 - refractory cytopenia with multilineage dysplasia and ringed sideroblasts (WHO 2008) in the Haematology Clinic of "Colentina" Hospital, Bucharest.

In November 2009 the patient was admitted in our clinic with severe anaemia and neutropenia, normal platelets count (Hb 7 g/dL with MCV 100.8 fL and reticulocytes 1%, WBC 2000/μL with 679 neutrophils/μL). The patient denies any significant history, no comorbidities and no exposure to chemical substances. Performance status at admission: ECOG scoring 1 based on the anaemic syndrome. B12 and folate serum levels were within normal range, serum ferritin: 680 μg/L (N:16.4–293.9) and a slight increase in serum erythropoietin 300 mU/mL (N: 2.4–33.0). Other laboratory tests presented no significant changes. The morphological examination of the peripheral blood and bone marrow (biopsy and aspirate) with immunohistochemistry and sideroblasts special coloration established the diagnosis of refractory cytopenia with multilineage dysplasia and ringed sideroblasts (about 20%), based on WHO classification (Figures 1 and 2). Cytogenetic examination revealed no modifications.

Results

Based on the scoring systems previously described, at diagnosis the patient was classified as follows: intermediate-1 (IPSS-1), intermediate (WPSS) and low risk (MDACC and MDS-CI) (Fig. 3, 4, 5, 6).

Variable	IPSS score*				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	< 5	5–10	–	11–20	21–30
Karyotype†	Good		Int.	Poor	
Cytopenias‡	0–1	2–3			

*IPSS risk groups: Low = 0; Int-1 = 0.5–1.0; Int-2 = 1.5–2.0; High = ≥ 2.5.
†Good = normal, -Y, del(5q), del(20q). Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies. Int. = other abnormalities.
‡Hb ≤ 10 g/dL; ANC ≤ 1.8 x 10⁹/L; platelets ≤ 100 x 10⁹/L.

Note: applies to newly diagnosed MDS, not secondary or previously treated MDS.

ANC = absolute neutrophil count

Greenberg P, et al. Blood. 1997;89:2079-88.

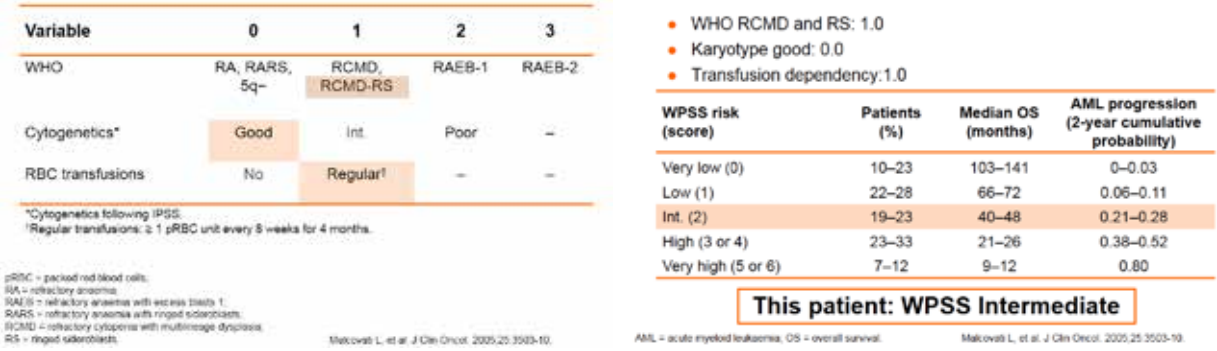
- Bicytopenia: 0.5
- Marrow blasts < 5%: 0.0
- Good karyotype: 0.0

Score	Subgroup	Median survival (years)	Died of leukaemia (%)
0	Low	5.7	19
0.5–1.0	Int-1	3.5	30
1.5–2.0	Int-2	1.2	33
> 2.0	High	0.4	45

This patient: IPSS Int-1 risk

Greenberg P, et al. Blood. 1997;89:2079-88.

Figure 3. International Prognostic Scoring System (IPSS): the patient enters the group risk intermediate-1 1 (IPSS Int-1 risk)



Variable	0	1	2	3
WHO	RA, RARS, 5q–	RCMD, RCMD-RS	RAEB-1	RAEB-2
Cytogenetics*	Good	Int	Poor	–
RBC transfusions	No	Regular†	–	–

*Cytogenetics following IPSS.
†Regular transfusions: ≥ 1 pRBC unit every 8 weeks for 4 months.

pRBC = packed red blood cells;
RA = refractory anaemia
RAEB = refractory anaemia with excess blasts 1;
RARS = refractory anaemia with ringed sideroblasts;
RCMD = refractory cytopenia with multilineage dysplasia;
RS = ringed sideroblasts.

Malcovati L, et al. J Clin Oncol. 2005;23:3503-10.

- WHO RCMD and RS: 1.0
- Karyotype good: 0.0
- Transfusion dependency:1.0

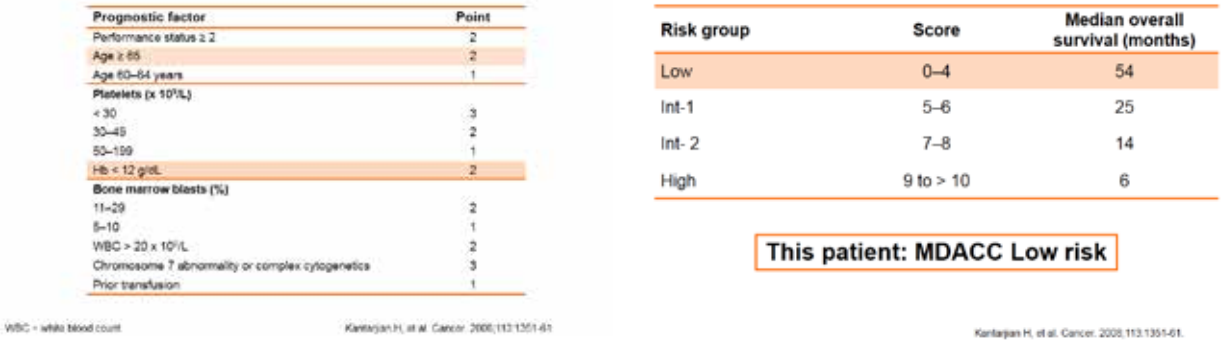
WPSS risk (score)	Patients (%)	Median OS (months)	AML progression (2-year cumulative probability)
Very low (0)	10–23	103–141	0–0.03
Low (1)	22–28	66–72	0.06–0.11
Int. (2)	19–23	40–48	0.21–0.28
High (3 or 4)	23–33	21–26	0.38–0.52
Very high (5 or 6)	7–12	9–12	0.80

This patient: WPSS Intermediate

AML = acute myeloid leukaemia; OS = overall survival.

Malcovati L, et al. J Clin Oncol. 2005;23:3503-10.

Figure 4. WHO Prognostic Scoring System: the patient enters the intermediate risk group (WPSS Intermediate)



Prognostic factor	Point
Performance status ≥ 2	2
Age ≥ 65	2
Age 60–64 years	1
Platelets (x 10^9/L)	
< 30	3
30–49	2
50–199	1
Hb < 12 g/dL	2
Bone marrow blasts (%)	
11–29	2
5–10	1
WBC > 20 x 10^9/L	2
Chromosome 7 abnormality or complex cytogenetics	3
Prior transfusion	1

WBC = white blood count

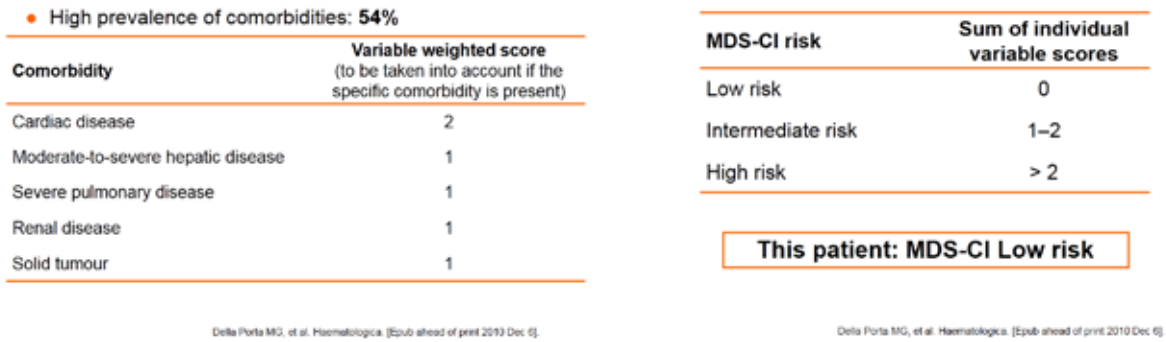
Kantarjian H, et al. Cancer. 2008;113:1351-61.

Risk group	Score	Median overall survival (months)
Low	0–4	54
Int-1	5–6	25
Int- 2	7–8	14
High	9 to > 10	6

This patient: MDACC Low risk

Kantarjian H, et al. Cancer. 2006;113:1351-61.

Figure 5. MD Anderson Scoring System (MDACC): the patient enters the low risk group (MDACC Low risk)



- High prevalence of comorbidities: **54%**

Comorbidity	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	2
Moderate-to-severe hepatic disease	1
Severe pulmonary disease	1
Renal disease	1
Solid tumour	1

Della Porta MG, et al. Haematologica. [Epub ahead of print 2010 Dec 6].

MDS-CI risk	Sum of individual variable scores
Low risk	0
Intermediate risk	1–2
High risk	> 2

This patient: MDS-CI Low risk

Della Porta MG, et al. Haematologica. [Epub ahead of print 2010 Dec 6].

Figure 6. MDS-specific Comorbidity Index (MDS-CI): the patient enters the low risk group (MDS-CI Low risk) [12]

The patient was initiated on red blood cells transfusions and erythropoietin. Shortly after, the patient became transfusion dependent, with an average of 3-4 erythrocytes units transfused per month.

One year after the diagnosis, the ferritin level increased to >1000 µg/L which led to introduction of iron chelation therapy with Deferasirox, at an initial dosage of 20 mg/kg/day, subsequently increased to 30 mg/kg/day (Fig. 7).

In September 2012 the bone marrow aspirate displayed: multilineage dysplasia with 25% ringed sideroblasts and erythroblastopenia, without residual thymic tissue at CT chest examination. Consecutively, we introduced Cyclosporine therapy at a dose of 5 mg/kg, and subsequent increase to 8 mg/kg, without haematological response. The transfusion demand increased to 6 units/month, and multiple hospital admissions. Progressively he developed left-ventricular dysfunction, secondary to severe anaemia and recurrent transfusions.

After approximately four years, in May 2013, the patient was still staged in an intermediate risk group (WPSS staging) but associated comorbidities (transfusion dependence and heart failure) included him in an increased risk group, based on MDS Comorbidities Index (MDS-CI Int - High risk), with low chances of survival. The bone marrow aspirate performed in May 2013 showed similar results as the previous one, respectively multilineage dysplasia and the presence of 20% ringed sideroblasts (Fig. 8).

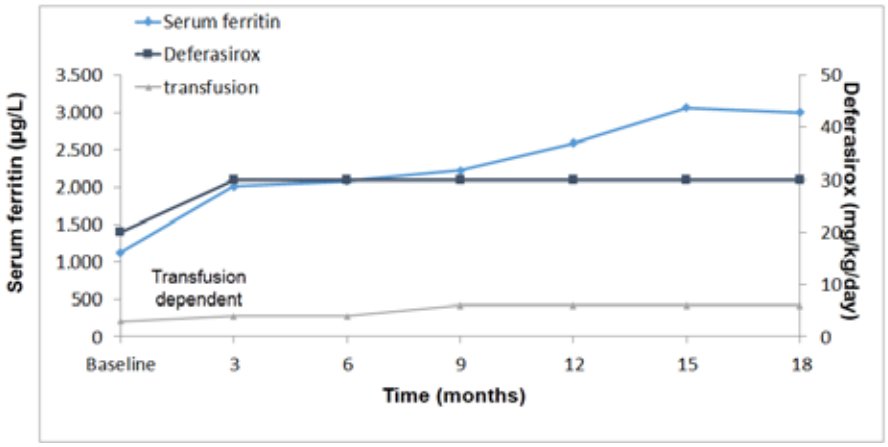


Figure 7. The patient's evolution under Deferasirox therapy

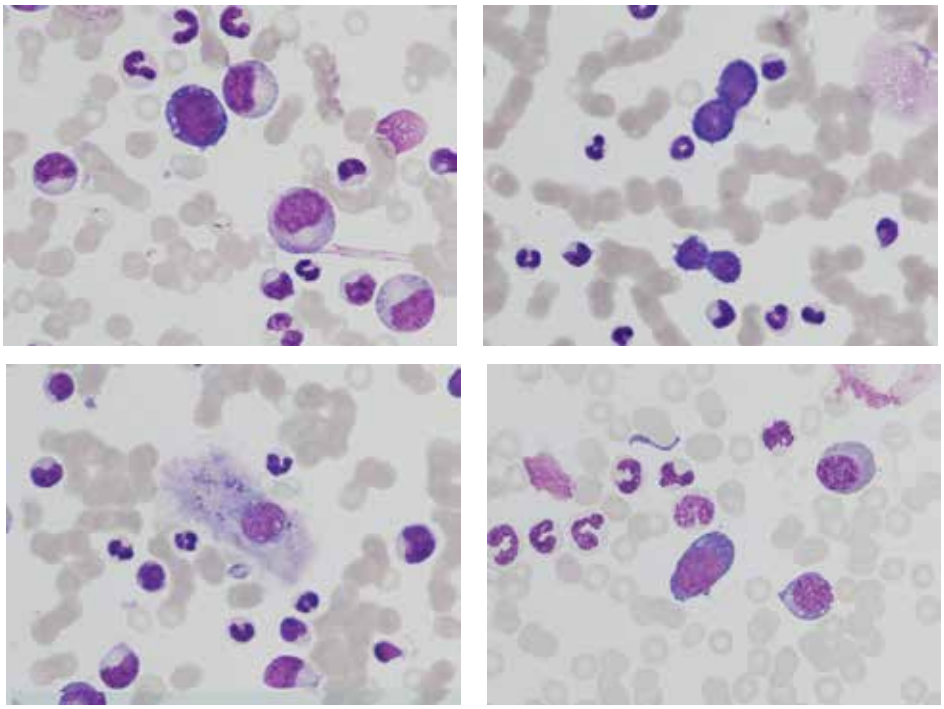


Figure 8. May 2013, May-Grünwald Giemsa stain, bone marrow aspirate: dyserythropoiesis, dysgranulopoiesis

Immunosuppression, severe anaemia with transfusion dependency and repeated hospital admissions had a significant impact on the prognosis.

In June 2013, the patient was diagnosed with staphylococcal endocarditis that led to his death, but no signs of leukemic transformation at that moment.

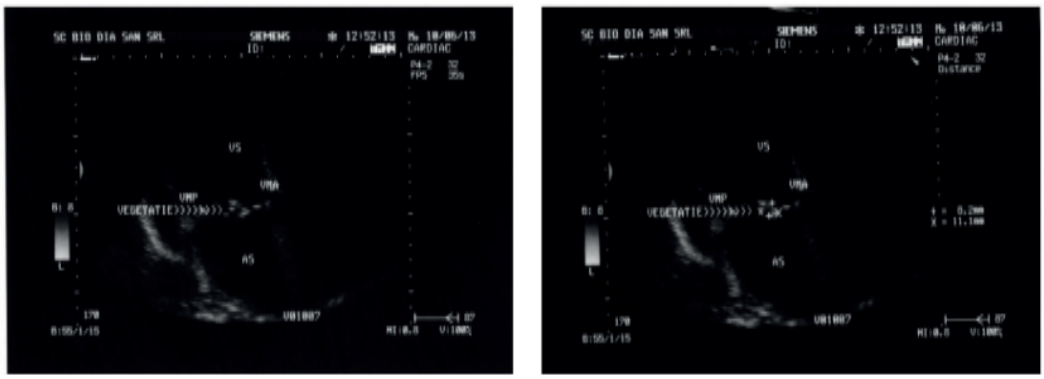


Figure 9. Posterior mitral valve vegetation revealed during the cardiac ultrasound examination

Discussions

The patient's new staging into an increased risk group, according to MDS

Comorbidities Index (MDS-CI Int - High risk) with low survival chances was confirmed by his death due to staphylococcal endocarditis, with no leukemic transformation. Thus it becomes clearer that in MDS patients staged in low or intermediary risk groups co-morbidities represent an independent risk factor that requires a reassessment of the current prognostic systems.

Conclusions

The diagnosis and staging of MDS patients in the correct risk groups help the medical staff to choose the appropriate therapy. However, for low risk MDS cases the evolution is heterogeneous and quite often influenced by comorbidities and not by leukemic transformation. In this context, various working groups in the world are trying to establish new risk models.

Aknowledgements *This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390/.*

The present article has been elaborated and written by Daniela Georgescu, MD and PhD student, since 2011, at UMF Carol Davila, Bucharest, under the coordination of Prof. Dr. Anca Lupu, MD PhD - Haematology Department.

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