Myelodysplastic syndrome and management of secondary hemochromatosis

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Summary

The indication for iron chelation in MDS should be determined only after careful consideration. Patients with "advanced MDS," those with a high percentage of blasts in the bone marrow or blood, generally do not live long enough to develop severe complications of iron overload. Thus, the use of iron chelators generally cannot help these patients.

In low-risk MDS, on the other hand, the situation is different. Here, ineffective erythropoiesis dominates the clinical picture. Patients with refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), or the 5q syndrome are often treated with erythrocyte transfusions for years. According to Schafer et al., regular transfusion therapy in adult patients can lead to glucose intolerance, focal portal hepatic fibrosis, and heart damage after less than four years of treatment. Iron chelation should be begun when the serum ferritin level exceeds 1000 ng/mL. Interestingly, the successful reduction of an iron overload can also improve bone marrow function.

Myelodysplasia is a term given to a spectrum of clonal myeloid diseases characterized by ineffective hematopoiesis, cytopenias, qualitative abnormalities of blood cells and the precursors, clonal chromosomal abnormalities and a variable degree of evolution to acute myeloid leukemia.

Refractory anemia, a category of myelodysplastic syndromes, is characterized by ineffective erythropoiesis, with normal or slightly decreased erythrocyte survival and minimal disturbance of the other cell lines maturation. The turn over of the serum iron is increased, but its incorporation into hemoglobin is reduced.

In the case of most patients, the disease remains stationary for a long time without symptoms of anemia, while a small percentage of them become addicted to repeated transfusions. This, in the absence of an appropriate prophylactic treatment, leads to iron overload and the development of hemochromatosis and its complications.

We present the case of a 77 years old patient, from urban environment, which appeared first at Fundeni Hematology Clinic in 2005 with moderate asthenia, fatigue, dyspnea at small efforts, discreet pallor, arthralgia. The patient was known with chronic ischemic heart disease, NYHA class II heart failure, mitral and tricuspid regurgitation grade II, glaucoma and dental infectious foci.

This was followed by regular assessments of blood counts in Fundeni Clinical Hematology , treatment with vitamin B1, B6, maintaining the Hb values over 8-9g/dl without transfusion requirement, until 2008 when the patient returned with pronounced symptoms and low Hb levels (<8 g / dl). We associated treatment with erythropoietin (with transient response) and monthly MER substitution (1-2 units / month).

The clinical examination in 2008showed average overall condition, mild asthenia and fatigue, pale skin, shortness of breath at small efforts, liver with the lower end sliding along the edge cost, no splenomegaly, holosistolic mitral and tricuspid murmurs grdII / VI, BP 130/80 mmHg, AV 80 bpm, moderate joint pain.

Investigations: Hb 7.5g/dl, Ht 23.4%, MCV 107.8fl, MCH 34.6pg, WBC 4090/mm ^{3} PLT 236.000/mm, monocytes 858/mm ^{3}, ret 1.3%, Mt1 N3 S30 E2 B1L42 M21 EBL 1 / 100, moderate anisocytosis, moderate poikilocytosis and hypochromia, hypogranular granulocytes, some with Pelger anomaly, platelet anisocytosis (see fig. 1)

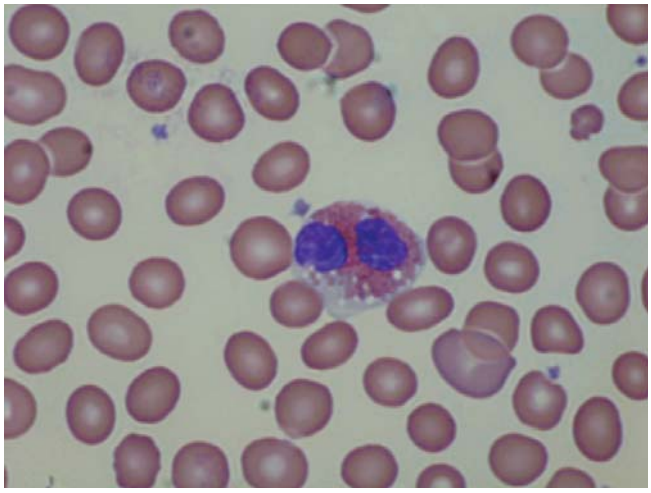

Fig. 1

Glucose **133**, liver and kidney functions-normal, levels of serum vitamin B12 and folic acid-normal, ferritin **796**μg / l, sideremie **235**, serum erythropoietin **118.7**

Myelogram: hypercellular marrow with erythroid hyperplasia and megaloblastic deviation, marked disgranulopoiesis, blasts absent (see fig. 2, 3) PBO:

spinal hipercelulara, panmieloza, diseritropoieza - HP aspect compatible with myelodysplastic syndrome RA/RARS HSMM moderately increased quantity SBL 60%, 6% ring SBL normal karyotype

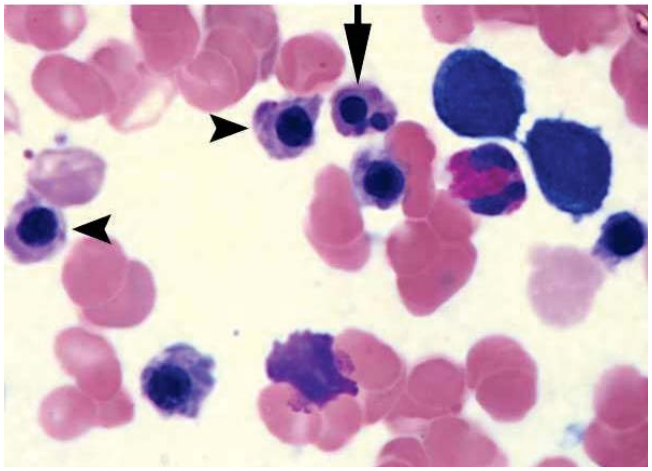

Fig. 2

-erythroblast on peripheral blood smear
-hipogranulare and pelgerisated granulocytes

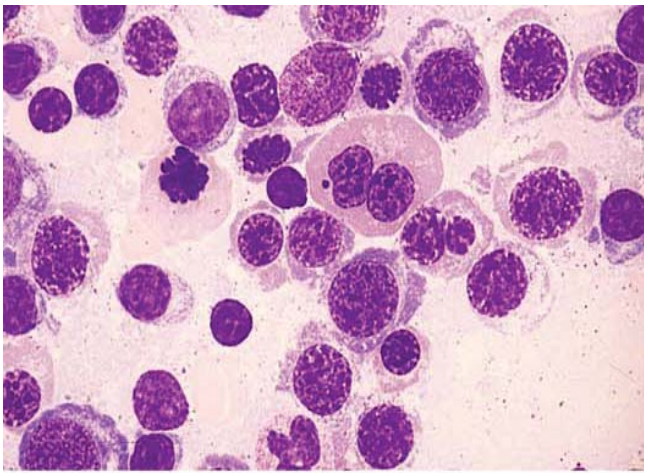

Fig. 3

-erythrocytes with megaloblastic changes
some binucleate and some in mitosis

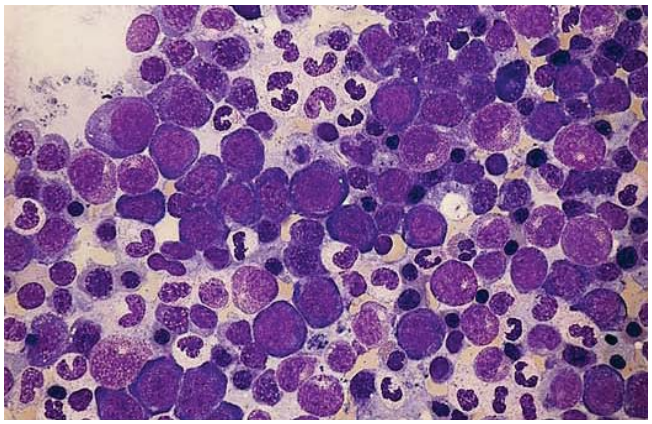

fig.4

-smear marrow with immature erythropoiesis
and megaloblastic changes
-absence of blasts and Auer rods

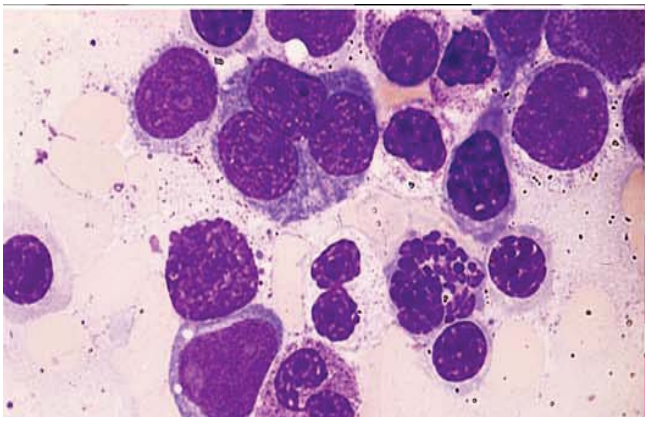

fig.5

-trinucleate proerythroblast
-atipical mitosis
-hypogranular granulocytes

Due to the concomitent heart disease and the associated symptoms accused by the patient (palpitations, fatigue, dyspnea on exertion), a cardiology evaluation was performed (may 2010): rhythmic heart sounds with frequent extrasystoles, left parasternal systolic murmur grd.III, minimal pretibiale swelling; **ECG**: sinus rhythm, 70 bpm, criteria for LVH voltage; **Echocardiogram**: severe pulmonary hypertension with slight dilatation of pulmonary artery, chambers size and function normal; mitral and tricuspid regurgitation grade II, slightly enlarged right ventricle, **Holter ECG** : frequent supraventricular extrasystoles, rare ventricular extrasystoles.

From 03.2010 we noticed a slight increase in transaminases and total bilirubin levels, maintaining a constant and slightly elevated blood glucose (130-170 mg/dl) and progressive increase in ferritin values (maximum of 5000 µg / l in march 2011). A high value of alpha fetoprotein (9.5ng/ml; N: 1.3-8) determined us to perform an abdominal CT examination (feb.2011) to exclude a possible digestive cancer. It highlights a liver size at the upper limit with nonhomogenous appearance, with inhomogeneous radial strips suggesting a fibrotic process, also a nodular hypodense image, 6mm, in the 6th segment of liver requiring MRI examination, bilateral hydronephrosis grade I-II.

Abdominal MRI (03.2011): diffuse loss in liver signal, changes consistent with the pathology of iron

storage. Also, the pancreas shows signal changes, materialized through a decrease in signal intensity by iron deposits. The liver appears to have the same density as the vertebral body (see fig. 6, 7).

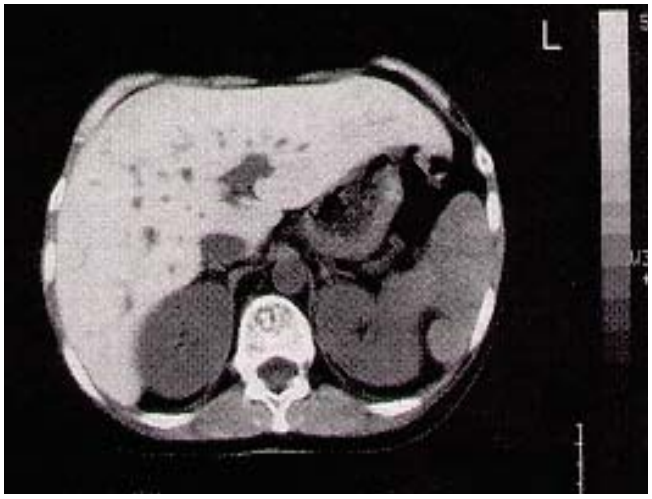

fig.6

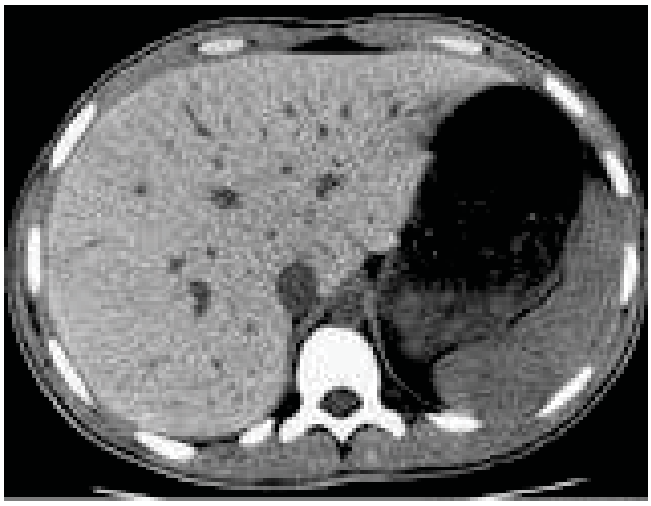

fig.7

The final diagnoses is: **myelodysplastic syndrome with refractory anemia score IPSS intermediate 1. Transfusion hemochromatosis. Heart failure. Type II diabetes. Extrasistolic arrhythmia - atrial fibrillation.** (see Table 1 WHO classification of the myelodysplastic syndromes)

Table 1

Table I. WHO classification for the myelodysplastic syndromes (Vardiman et al., 2002).

Category	Peripheral blood	Bone marrow
RA	Anemia Blasts <1% Monocytes <1,000/µl	Erythroid dysplasia Blasts <5% Ring sideroblasts <15%
RARS	Anemia Blasts <1% Monocytes <1,000/µl	Dysplasia only in the erythroid line Ring sideroblasts ≥15% Blasts <5%
RCMD	Cytopenias (bi- or pancytopenia) Blasts <1% Monocytes <1,000/µl	Dysplasia ≥10% of the cells Blasts <5% Ring sideroblasts <15%
RCMD-RS	Cytopenias (bi- ou pancytopenia) Blasts <1% Monocytes <1,000/µl	Dysplasia ≥10% of the cells Blasts <5% Ring sideroblasts ≥15%
RAEB-I	Cytopenias Blasts <5% Monocytes <1,000/µl	Dysplasia uni- or multilines Blasts 5-9%
RAEB-II	Cytopenias Blasts 5-19% Monocytes <1,000/µl Auer rods ±	Dysplasia uni- or multilines Blasts 10-19% Auer rods ±
5q- syndrome	Anemia Blasts <5% Normal or increased platelet counts	Megakaryocytes hypolobulate normal or increased Blasts <5% del(5q) alone
MDS without classification	Cytopenias Blasts <1%	Single line dysplasia of the granulocytes or megakaryocytes Blasts <5%

RA, refractory anemia; RARS, RA with ring sideroblasts; RCMD, refractory cytopenia with multiline dysplasia; RCMD-RS, RCMD with ring sideroblasts; RAEB, RA with excess blasts; MDS, myelodysplastic syndrome.

Tabel 2 (MDS classification according to the IPSS)

Variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Number of types of blood cells affected	0/1	2/3			

Elements suggestive of diagnosis:

macrocytic anemia, abnormal erythrocyte and granulocyte morphology on peripheral blood smear, the presence of erythroblast in the periphery; diseritropoietic marrow
- Hypercellular marrow contrasting with poor periphery
- increased iron deposits (ferritin level and bone marro hemosiderin
- Increased serum erythropoietin
- normal serum levels of vitamin B12 and folic acid
- MRI appearance, echocardiogram, hepatocytolysis, hyperglycemia

For the certain diagnosis of hepatic iron storage, a liver biopsy would be necessary (not done at our patient). It would show the presence of brown granular deposits in the hepatocytes and Kupffer cells (fig.8, 9). It could also evaluate the concentration of iron / g dry weight (N <1.5mg / g)

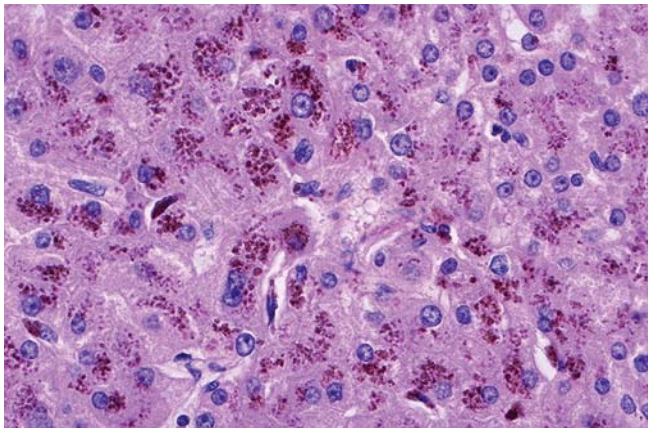

fig. 8

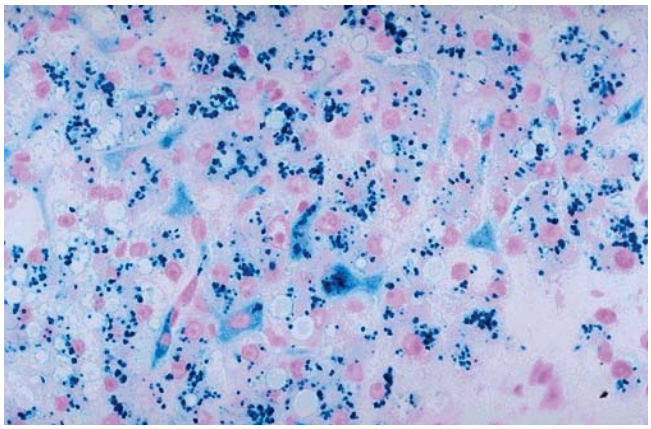

fig.9

-haemosiderosis = relatively benign accumulation of iron
-hemochromatosis = term used when dysfunction of the affected organ occurs.

After the imaging evaluation of the patient, the elevated transaminases and blood sugar levels can be considered to be in the context of secondary hemochromatosis of liver and pancreas after repeated transfusions of (each unit of blood transfused provides 250 mg of iron). Given the joint symptoms and cardiac exploration tests, we might assume that the arthropathy, heart failure and arrhythmia are all consequences of iron overload.

Taking into account the patient's age, comorbidities, permanent need of transfusions, this secondary alteration of liver, pancreatic and cardiac functions and possibility of future complications (20-30% may develop liver carcinoma, diabetes, cardiomyopathy) is **absolutely necessary to initiate treatment with iron chelators.**

The main objectives of treatment:

1. ensure the quality of life;
2. decrease transfusion requirements;
3. removing of both iron-free and excess iron from tissues and organs and reducing associated long-term toxicity;
4. long-term survival.

Clinical case management: therapeutic strategy

a) replacement therapy to relieve symptoms of anemia and decrease the risk of angina pectoris to old patient with multiple cardiac comorbidities; We tried to maintain Hb above 8g/dl with 1-2 units of erithrocytes/ month.

b) administration of recombinant human erythropoietin to decrease transfusion requirements and, therefore, the body iron load. We started with darbepoetin alfa 500 mcg every 3 weeks, then 500 mcg every 10 days, but without a satisfactory response. The same was tried with Epoietinum beta dose of 30,000 U / week.

Treatment of secondary hemochromatosis is made with iron chelators by injection (deferoxamine 20-60 mg / kg 5 days / week) or, more convenient for the patient, orally (deferasirox). We initiated therapy with standard dose **EXJADE 20** mg / kg (1500 mg / day) administered in single dose on an empty stomach, 30 minutes before meals, dispersed in a glass of water or orange juice. Is necessary to monitor the levels of creatinine and transaminases before the start of therapy, then monthly throughout treatment. It is also required monthly monitoring of serum ferritin levels and to adjust the dose of Exjade according to that. If the ferritin falls below 500 mg / l, the administration is discontinued.

According to FAB classification of myelodysplastic syndromes, refractory anemia enjoys a survival of approximately three years and a low rate of transformation to AML (~ 12%). See table below:

TABLE 2: Main features of MDS according to the FAB classification

FAB subgroup	BM blasts (%)	Ringed sideroblasts (%)	PB monocytes ($\times 10^9$/L)	Chromosomal abnormalities (%)	Frequently associated karyotype	Rate of leukemic progression (%)	Median survival (mo)
RA	< 5	< 15	< 1	30	5q-, -7, +8, 20q-	12	32
RARS	< 5	≥ 15	< 1	20	+8, 5q-, 20q-	8	42
RAEB	5–20	Variable	< 1	45	-7, 7q-, -5, 5q-, +8	44	12
RAEB-t	21–30	Variable	Variable	60	-7, 7q-, -5, 5q-, +8	66	5
CMML	1–20	Variable	≥ 1	30	-7, +8, t(5;12), 7q-, 12q-	14	20

BM = bone marrow; CMML = chronic myelomonocytic leukemia; FAB = French-American-British; MDS = myelodysplastic syndromes; PB = peripheral blood; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-t = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts

In terms of clinical evolution, patient's general condition remained satisfactory, according to the degree of anemia (asthenia, fatigue) and medication tolerance. During treatment the hepatic and renal functions was repeatedly assessed (AST level, ALT slightly regression, creatinine within normal limits), as well as glucose levels (values between 100-130 mg / dl). Ferritin decreased from 5000 mg / l to ~ 900µg / l in a few months. Patient will repeat MRI in 6 months to estimate the iron load in the affected organs after chelation therapy. Cardiologic, ophthalmologic and audiometric reevaluation will be done every12 months as recommended. Any adverse effects of therapy with Exjade will be recorded and properly treated (for our patients: bowel slightly accelerated - proper hydration, proper diet, epygastralgia and dyspeptic syndrome - Omeprazole, NoSpa; moderate neutropenia - infection prophylaxis, antibiotic treatment if needed).

In conclusion we have presented the case of a 77 years old patient, diagnosed with myelodysplastic syndrome (refractory anemia) with an intermediate IPSS score, with longterm evolution and a history of ~ 3 years of replacement therapy, who developed iron overload which had materialized into a liver, pancreas and heart malfunction. We initiated therapy with iron chelators in order to reduce the deposits of ferric pigment and decrease the risk of developing severe and irreversible complications (liver carcinoma, insulin-requiring diabetes, cardiomyopathy and heart rhythm disturbances). Patient's evolution was favorable, with decreasing serum ferritin level (in the context of continued therapy monthly MER) and improving liver and pancreatic function.

Given the intermediate score with longer survival, the high risk of developing toxicity caused by accumulation of organic iron (it is known that for every 500 mg / l ferritin above 1000 mg / l the risk of death increases by ~ 30% and iron chelation therapy almost doubles the overall survival in patients with IPSS 0-1).

All of this underscore the need for early initiation of treatment with iron chelators at optimal doses.

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