Sarcoidosis in a patient with 5q- syndrome

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Abstract

We present the case of a 59-years-old male who was first admitted to our clinic in July 2011 with pallor, weakness, fatigue, dizziness and pain in the left upper quadrant. A clinical and biological diagnosis of Myelodysplastic syndrome- RAEB1 with del(5q) was made. Treatment was initiated with low doses of Cytarabine in association with Epoetinum beta, but with no marrow response. He obtained complete hematological response after one course of "3+7" regimen. There was no need for further therapy. Within one year, the patient returned with cough, dyspneea, pallor, skin lesions, eye dryness and redness. A CT exam of the chest revealed mediastinal lymph nodes. After biopsy, the diagnosis of sarcoidosis was established. He is now under corticotherapy, with good response and just begun treatment with Lenalidomide.

This case illustrates the predisposition for sarcoidosis created by the deletion of key genes on the long arm of chromosome 5. Research on this association is recommended.

Introduction

Sarcoidosis (Besnier-Boeck-Schaumann disease) is a multisystem inflammatory illness that involves abnormal collections (noncaseating granulomas) in multiple organs, most often in the lungs and intrathoracic lymph nodes, but any organ can be affected.

T cells play a central role in the development of sarcoidosis, as they propagate an excessive cellular immune reaction. This picture may explain its association with several blood diseases like lymphoma, leukemia, multiple myeloma and myelodysplasia. 5q- syndrome has been showed to predispose to the development of sarcoidosis due to an imbalance in the cytokine pool and repeated interactions between macrophages, T-cells and B-cells. These phenomenons may be caused by the deletion of genes coding for T helper cell 2 cytokines, situated on the long arm of chromosome 5.

5q- syndrome is a distinct type of myelodysplasia with a medullary blast count less than 5% and a isolated deletion of the long arm of chromosome 5, including bands q31-q33. This region also carries the gene coding for T helper cell 2 cytokines (IL3, IL4, IL5, GM-CSF). A special attention should be given to those patients not correctly defined as 5q- syndrome: they have either excess blasts or additional karyotypic abnormalities. They do not have a good prognosis, unlike the one with isolated del(5q).

In 2005 Lenalidomide was approved by the FDA for the treatment of patients with transfusion dependent anemia due to low/intermediate 1 risk MDS associated with a deletion 5q with or without additional cytogenetic abnormalities.

Case presentation

We present the case of a 59-years-old male, J.E., smoker, with a history of large hiatal hernia, colonic diverticulosis, left renal lithiasis and internal hemorrhoids, who was first admitted to Emergency Military Hospital complaining of pallor, pain in the left upper quadrant, weakness, fatigue and dizziness. The local blood tests revealed the presence of mild anemia (Hb 10.4 mg/dl) and leucopenia (WBC 2900/mm3), a mild rise in serum creatinine and uric acid; an abdominal ultrasound showed hepato-splenomegaly. A bone marrow aspirate was performed and the result suggested the diagnosis of myelodysplasia.

He was referred to our clinic in Jul 2011 for further investigations, with the same symptoms. The only abnormalities at the physical examination were pallor and mild splenomegaly.

The laboratory studies showed no significant changes compared to the patient's previous results, except for high levels of feritin (158.4 ng/dl) and serum EPO (59.4 mU/ml).

A bone marrow aspirat (Fig. 1 and 2) and biopsy confirmed the diagnosis of myelodysplastic syndrome – RAEB1 (WHO), blasts 7-8%. The biopsy also found the presence of multiple, small, paratrabecular granulomatous lesions, without necrosis, one of which containing a giant multinuclear cell. The Ziehl-Neelson test was negative.

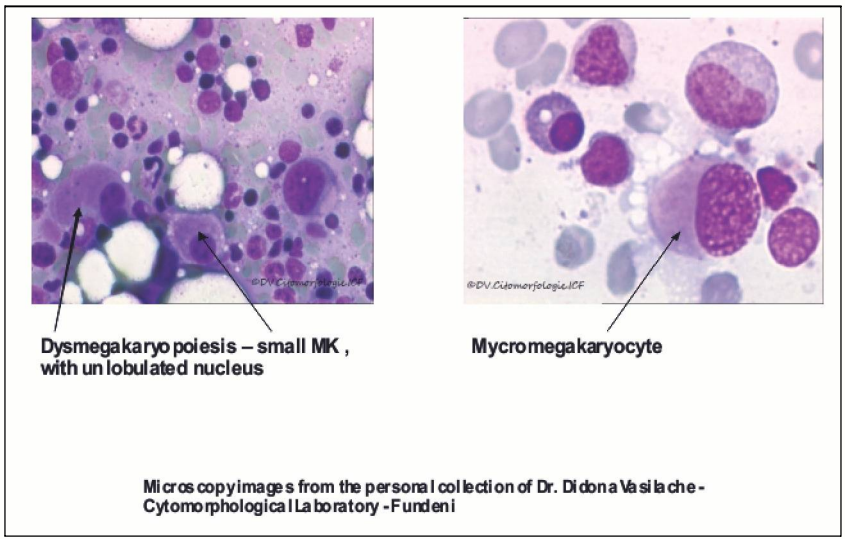


Fig. 1

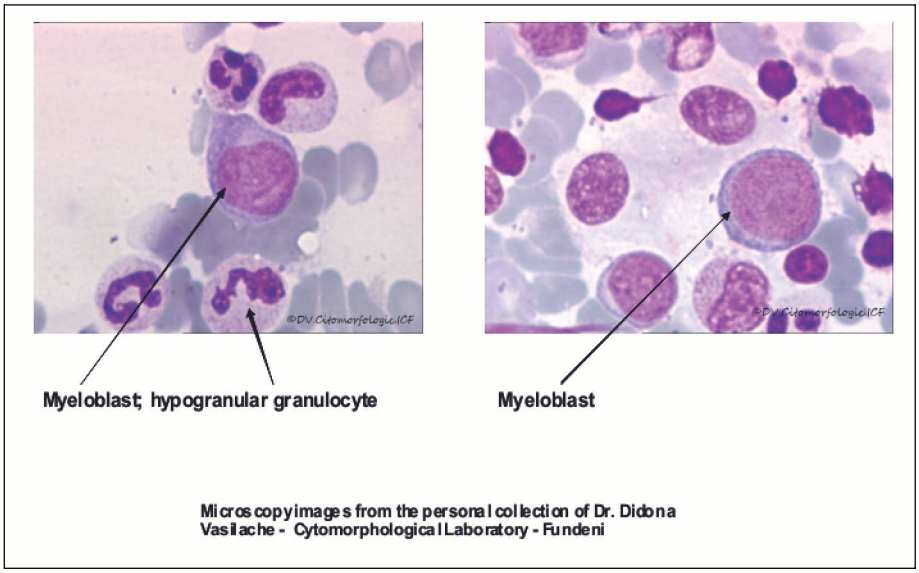


Fig. 2

Due to the temporary unavailability of the karyotype studies at that moment, we tested the patient for the deletion of 5q by FISH, at the Medical Genetic Laboratory of "Victor Babes" Institute. The test was positive for the presence of q31.1 deletion, in 24 of the 56 analised metaphases. (Fig. 3)

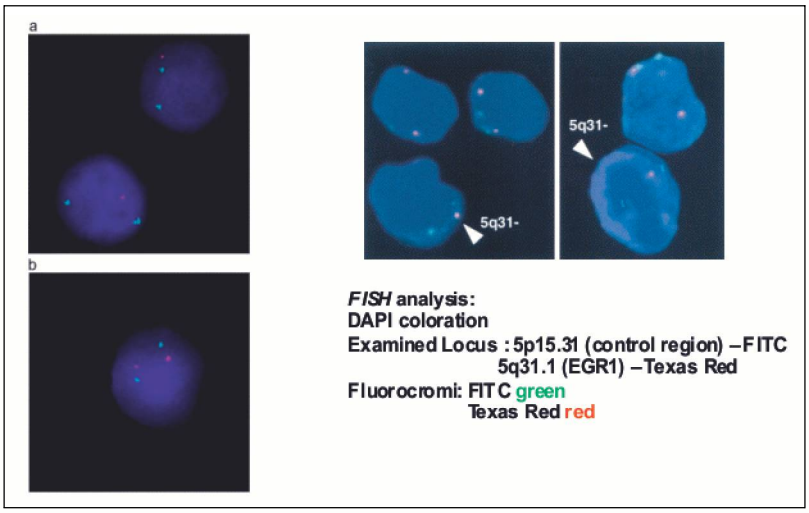


Fig. 3

One month later we performed the cytogenetic analysis and we discovered other abnormalities besides del(5q) (Fig. 4):

46,XY(4)
46,XY,del(5)(q)[3]
92,XXY,…[2]
174,XXXYY,…[2]
146,XXYY,…[2]

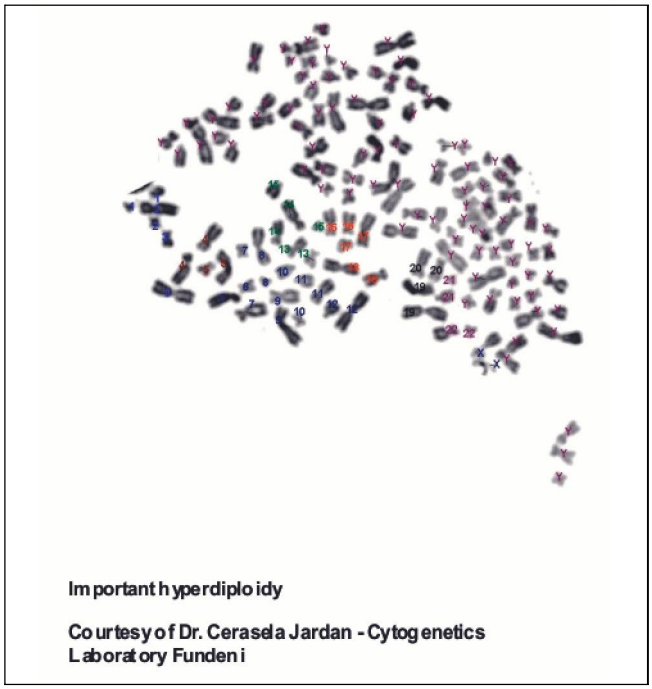
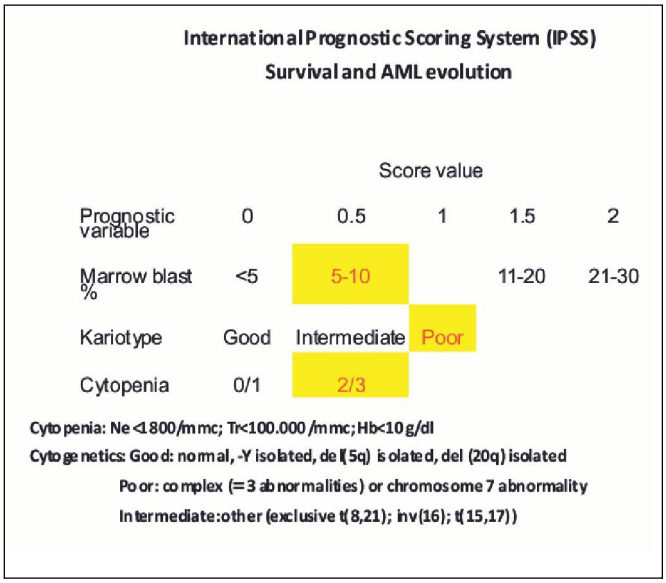
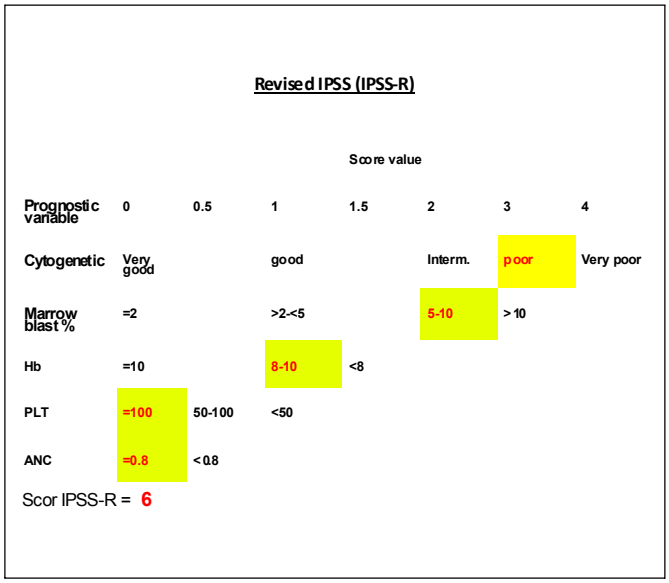


Fig. 4

Due to this findings, we concluded that the patient had MDS-RAEB1, IPSS INT-2, IPSS-R high, with unfavorable prognosis in the absence of therapy.





According to the NCCN Guidelines for the Myelodysplastic Syndrome for not high-intensity therapy candidate, the first line treatment was Azacitidine (preferred) or Decitabine (Fig. 5). But none of them was available in our hospital and the patient did not have the financial possibility to obtain them.

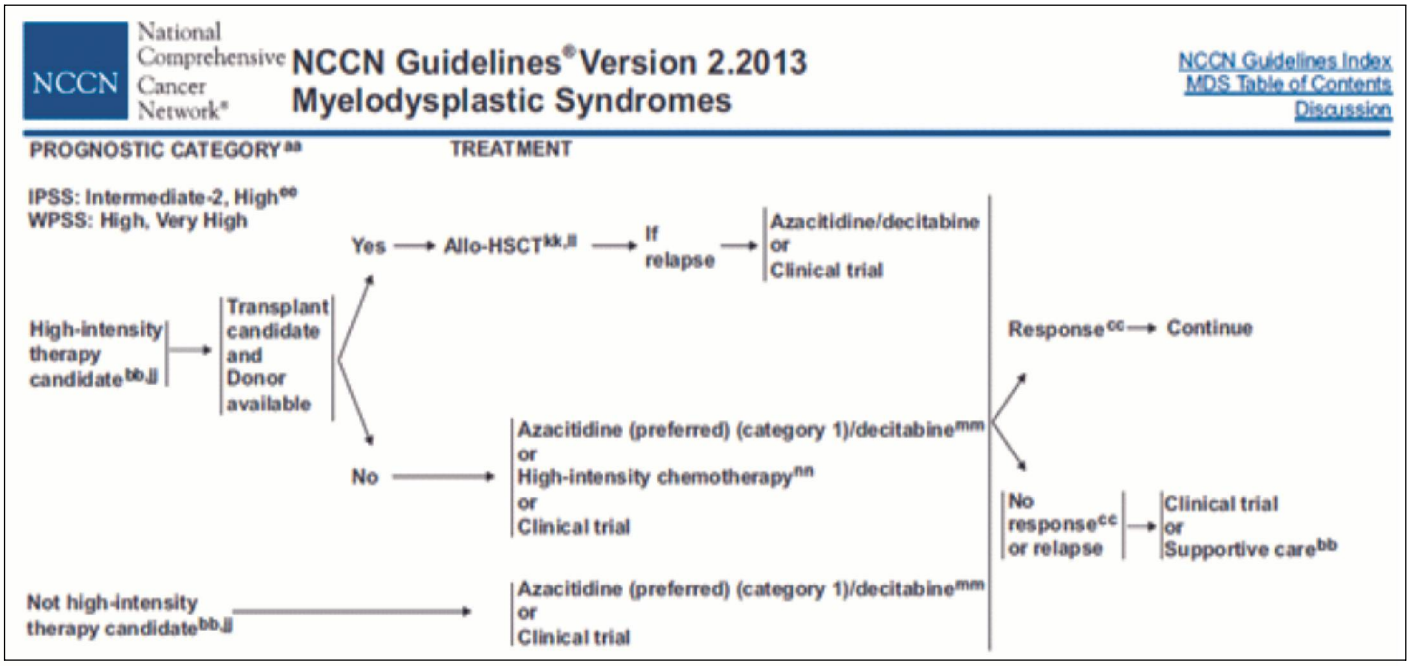


Fig. 5

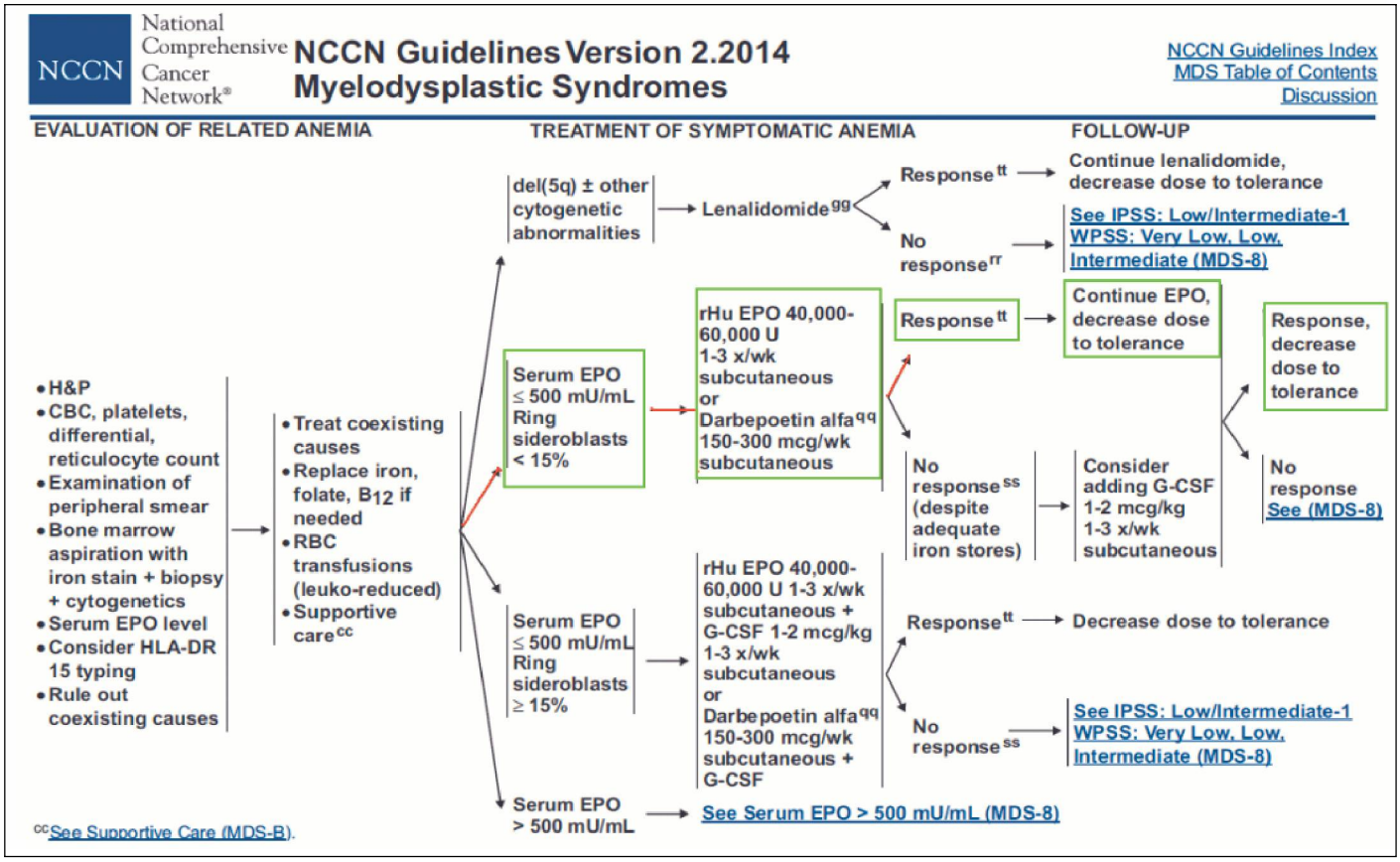


Fig. 6

In this circumstances, we begun to treat him with subcutaneous small doses of Cytarabine (30mg/day, 7 days) along with weekly administration of Epoetinum beta 30.000 UI (Fig. 6); the patient responded well, with a rapid rise in Hb levels (from 6.3 to 12.6 mg/dl in 4 months), but with the persistence of leucopenia and marrow blasts >5%. So, in March 2012 the patient received a more intensive chemotherapy (Cytarabine 100

mg/m2/day 7 days + Epirubicine 45 mg/m2/day 3 days) well tolerated and with no major complications. The marrow response was good, with a residual blast population of 2-3%. The patient remained under a close supervision, with regular bone marrow evaluations and with no further therapy. He no longer needed the administration of rHu EPO, the Hb levels maintaining within normal limits and the general condition of the subject being excellent.

Everything went well until early 2013 when the Hb begun to fall, the patient feeling progressively weak and dizzy. No further cytopenias developed beside anemia (Hb 9.6-8.2 mg/dl). The marrow showed no increase in blast percentage. The cytogenetic examination (Oct 2013) indicated only the presence of del(5q) abnormality (so 5q- syndrome at this moment?):

46,XY[11]
46,XY,del(5)(q)[5].

The WPSS at this stage was 0 (MDS 5q-, good karyotype and no transfusion requirement) (Fig. 7). The NCCN Guidelines recommended treatment with Lenalidomide (Fig.8), also not available in our country. We choosed to keep the patient under close surveillance, weekly Epoetinum beta and monthly evaluation of the hematologic parameters.

The WHO classification -based Prognostic Scoring System (WPSS) for myelodysplastic syndromes (MDS)

Prognostic Variable	Score Value				
	0	1	2	3	
WHO category	RA, RARS, del(5q)	RCMD, RCMD-RS	RAEB-1	RAEB-2	
Karyotype*	Good	Intermediate	Poor	--	
Transfusion requirement†	No	Regular	--	--	
	WPSS Risk Category‡				
	Very Low	Low	Intermediate	High	Very High
Median overall survival, mos	141	66	48	26	9
AML progression, cumulative probability					
2 yrs	0.03	0.06	0.21	0.38	0.80
5 yrs	0.03	0.14	0.33	0.54	0.84

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Red blood cell transfusion dependence was defined as having at least 1 red blood cell transfusion every 8 wks over a period of 4 mos.
‡Based on validation cohort.

Fig. 7

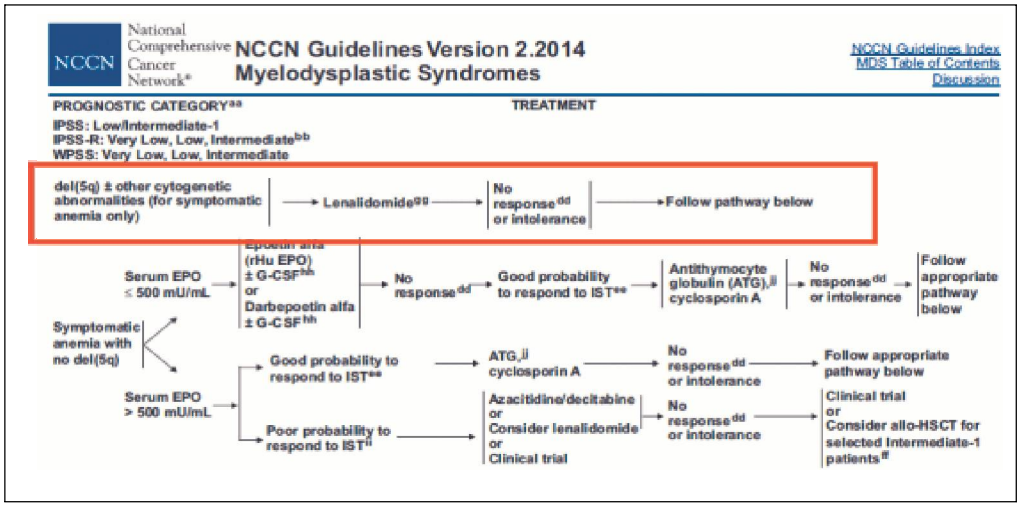


Fig. 8

Since 05.2013 he also begun to experience hacking cough, shortness of breath, eye dryness and redness, lack of energy and several macula-papular eruption on the skin. A dermatologic examination could not determine the cause of the skin lesions; topical ointments were unsuccesfull. The ophthalmologist suspected a more complex explanation for all the symptoms: a systemic inflammatory disease with multiple organ involvement – sarcoidosis.

The chest X-ray detected mediastinal lymph nodes so he was referred to the Pneumophtisiology Institute "Marius Nasta" for further investigations. The chest CT confirmed the presence of meddiastinal adenopaties. The patient underwent anterior mediastinoscopy Carlens type, with lymph node biopsy. The diagnostic of sarcoidosis (with pulmonary, skin and eye involvement) was established.

He begun corticotherapy, with favorable evolution.

But in Jan 2014 he started to experience worsen of the anemia (Hb 6.3 mg/dl) and the related symptoms (asthenia, fatigue, dyspnea). He received transfusions regulary, 1-2 units/month, concomitent with weekly Epoetinum.

In these conditions, we preceeded with the search for Lenalidomide, a very efficient drug for the treatment of 5q- syndrome. The patient managed to obtain it from abroad and on 1st Jul he begun to take 10 mg/day, 21 days/month.

We are looking forward to evaluating the patient's response.

Conclusions

1. 5q-syndrome must be differentiated from other forms of MDS with del (5q) with higher blast percentage in bone marrow and / or other associated cytogenetic abnormalities. They have a worse prognosis and benefit from more aggressive therapies;
2. 5q31 FISH analysis is useful, but not sufficient for diagnosis; it should be made in suspected cases of 5q-syndrome if cytogenetic study is inconclusive or with no metaphases. Cytogenetic testing will be required for confirmation
3. Urgent steps must be taken to introduce on the list of drugs reimbursed by the National Insurance Agency of new molecules that have proven efficacy in treating certain myelodysplastic syndromes (azacitidine, decitabine, lenalidomide) so that they would be available to our patients.
4. 5q-anomaly can create a favorable ground for the development of immune imbalances which in turn can trigger complex disorders. Is also the case of sarcoidosis, a multisystem inflammatory disease that can have major repercussions on the health of the patient
5. Treatment with Lenalidomide may induce cytogenetic remission and consequently an improvement of the disturbance in the cytokine pool and the inflammatory processes that appear in sarcoidosis.

References:

1. Martin Jadersten and Aly Karsan, "Clonal evolution in myelodysplastic syndromes with isolated del (5q): the importance of genetic monitoring"; Haematologica 2011 96(2) 177-180;
2. Jacqueline Boultwood, Andreea Pellagatti, Andrew McKenzie and James Wainscoat, "Advances in the 5q- syndrome", Blood, 2010, volume 116, number 26
3. Mario Cazzola, "Myelodysplastic syndrome with isolated 5q deletion (5q- syndrome). A clonal stem cell disorder characterized by defective ribosome biogenesis", Haematologica, 2008; 93(7), 967-972;
4. "Pathology of Myelodysplastic syndromes associated with isolated del 5q", Medscape
5. NCCN Guidelines for the Myelodysplastic Syndrome
6. Pierre Fenaux and Charikleia Kelaidi, "Treatment of the 5q- syndrome", ASH Education Book, January 1, 2006, vol. 2006 no1, 192-198;
7. Alan List et al, "Lenalidomide in the Myelodysplastic syndrome with chromosome 5q deletion", The New England Journal fo Medicine 2006; 355: 1456-1465.