

CASE REPORTS

Refractory anemia with ringed sideroblasts and thrombocytosis without JAK2 V617F mutation: report of three cases

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Abstract

In the *WHO* classification, there is a provisional entity called Myelodysplastic/Myeloproliferative Neoplasm, Unclassifiable (MDS/MPN, U). Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T) was included in this category. Recently published studies report a small percentage of patients with RARS-T. Sixty percent of these have JAK2 V617F mutation, which can suggest the coexistence of two pathological conditions (MDS and MPN). In this paper, we analyzed three patients diagnosed with RARS-T in the Department of Hematology, "Fundeni" Clinical Institute, Bucharest, Romania, during the period 2005–2011. The patients were investigated with cytogenetic exam and molecular biology. In these three cases were identified morphological features of multilineage dysplasia (two-lineage dysplasia in two cases and three-lineage dysplasia in one case). In two cases, thrombocytosis was under $1000 \times 10^3/\mu\text{L}$ and clinical evolution was similar to the myelodysplastic syndrome (transfusion dependent anemia with response to administration of erythropoietin). In the third case, the platelets were over $1000 \times 10^3/\mu\text{L}$ and with response to the treatment with Hydrea, which improved anemia. JAK2 V617F mutation was not identified in any case. RARS-T remains a provisional entity and requires a complex investigation of patients for the correct diagnosis of these patients. Therapeutic options should be personalized to each case in part because there is not yet a standardized treatment of these patients.

Keywords: Myelodysplastic Syndrome (MDS), Myelodysplastic/Myeloproliferative Neoplasm (MDS/MPN), Refractory anemia with ringed sideroblasts with thrombocytosis (RARS-T).

Introduction

Myelodysplastic Syndromes (MDS) are a group of heterogeneous clonal stem cell disorders characterized by ineffective hematopoiesis, hypercellular bone marrow, one or more cytopenias in peripheral blood, dysplastic changes in one or more myeloid cell lines identified in bone marrow (BM) and peripheral blood (PB) and genetic instability. Evolution may be indolent or can progress quickly to acute myeloid leukemia, depending on the subtype of MDS [1–3].

In the *WHO* classification, there is a group called Myelodysplastic/Myeloproliferative Neoplasm, Unclassifiable (MDS/MPN, U) which include chronic myelomonocytic leukemia (CMML), juvenile CMML (JCMML), atypical chronic myeloid leukemia (ACML) BCR-ABL1 negative and MDS/MPN, U. RARS-T is included in the category of MDS/MPN, U [4]. This is a provisional new entity characterized by clinical and morphological features common to both MDS and the CMPN (chronic myeloproliferative neoplasms), but it could not be introduced in none of these entities. It is not known yet if RARS-T is a distinct entity, an evolution of RARS associated with additional genetic defects or there are two entities associated in the same patient [4].

RARS-T is a rare entity and the current studies are done on small groups of patients. Patients have hypercellular bone marrow, dysplastic changes on one or more myeloid cell lines, ringed sideroblasts over 15%, abnormal megakaryocytes similar to those from Essential Thrombocythemia (ET), reticulin fibrosis. Clinically, patients can present splenomegaly [5–7]. Thrombocytosis is in general more than $600 \times 10^3/\mu\text{L}$.

In the described cases, it was found that 60% of the patients had JAK2 V617F mutation. Less commonly in RARS is MPL W515 T/L mutation [8–11]. JAK2 V617F mutation is point somatic present in cytoplasmic Janus Kinase 2 (JAK2). Mutation consists in replacing the valine with phenylalanine in the position 617 with the activation of the JAK2 tyrosine kinase and, thereby, STAT5 phosphorylation. The appearance of this mutation is involved primarily in the pathogenesis of CMPN Ph negative (in 90% of cases of polycythemia vera, in 40% of cases of ET, in 50% of cases of idiopathic myelofibrosis), but also in other hematological disorders [12]. In MDS is very rare and has a greater frequency in MDS/MPN, U [13].

Due to the low incidence in RARS-T, cannot make a

correct estimation of overall survival and transformation into acute myeloid leukemia. A retrospective analysis performed on 23 patients showed a median survival at five years, 86% compared to 62% in patients with JAK2 V617F mutation without JAK2 V617F mutation [14].

☞ Patients, Methods and Results

We present three cases diagnosed with RARS-T in the Department of Hematology, “Fundeni” Clinical Institute, Bucharest, Romania, during the period 2005–2011. The study was conducted according to the Declaration of Helsinki and patients had signed consent. The patients were investigated with cytogenetic exam and molecular biology. Investigation protocol included: the complete blood cell count (CBC), bone marrow examination (aspirate and biopsy), cytogenetic examination, FISH for del(5q) in one case, tests of molecular biology (JAK2 mutation in all cases, the BCR-ABL in two cases and PDGFR in one case). Causes of secondary thrombocytosis have been excluded.

Case No. 1

The first case is a 23-year-old female patient, which was presented to the physician in May 2010 for moderate fatigability, headache, paleness, no adenopathy, and no organomegaly.

The peripheral blood showed macrocytic anemia: hemoglobin (Hb) 4.2 g/dL, hematocrit (Ht) 12.7%, mean corpuscular volume (MCV) 130 fL, white blood cells (WBC) $4.2 \times 10^3/\mu\text{L}$ (neutrophils 58%, lymphocytes 38%, monocytes 4%), platelets (Plt) $657 \times 10^3/\mu\text{L}$; anisocytosis with macrocytosis, poikilocytosis (ovalocytes, dacriocytes), basophilic stippling, hypogranular neutrophils.

Serum erythropoietin 649.8 mIU/mL (normal values 3–16.6 mIU/mL), lactic dehydrogenase (LDH) 261 IU/L (normal values <190 IU/L), serum B₁₂, folic acid, iron, ferritin, liver and kidney tests were in normal ranges. Platelet aggregation assays in normal range.

BM aspirate: hypercellularity, granulocytic lineage 69% with 1% myeloblasts and dysgranulopoiesis (hypogranular, hypolobated neutrophils – pseudo Pelger–Huet anomaly), erythroid lineage 22%, with dyserythropoiesis (megalo-blastic changes, Cabot rings, Howell–Jolly bodies), megakaryocytic hyperplasia, dysmegakaryopoiesis (large multinucleated forms and micromegakaryocytes). Ringed sideroblasts over 15%. The diagnosis was compatible with MDS/MPN type RARS-T.

BM biopsy: MDS with blasts under 5%, megakaryocytic hyperplasia, dysmegakaryopoiesis – MDS/MPN (Figure 1).

Cytogenetic exam: 47,XX, +8 in 100% of metaphases.

FISH del(5q), JAK2 V617F mutation negative, BCR-ABL1, PDGFR negative.

The patient received treatment with low molecular weight heparin (Clivarin), antiaggregant therapy (Aspenter), Anagrelidum, transfusion with red blood cells. Soon, the patient became transfusion dependent (2–4 units of red blood cells/monthly). At eight months from diagnosis, ferritin increased to 1020 $\mu\text{g/L}$ and iron chelation treatment started (Exjade).

Repeating the bone marrow examination, at 12 months

after diagnosis shown a stationary state, without progression of the disease.

The period of the follow-up was 32 months.

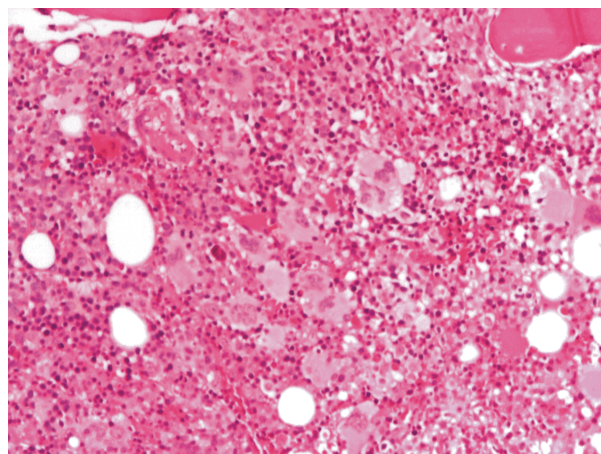


Figure 1 – Hypercellular bone marrow, with pan-myelosis; dyserythropoiesis; clusters of polymorphous megakaryocytes (MK). Bone marrow, Hematoxylin–Eosin (HE) staining, ob. $\times 10$.

Case No. 2

The second case is a 34-year-old woman patient diagnosed as a child with heterozygous β thalassemia, bilateral cataracts, bilateral atrophy of optic nerve (pathology diagnosed the patient's mother).

The patient was known with moderate anemia, well-tolerated (Hb around 10 g/dL), splenomegaly, but without the transfusion necessary, with good performance status (IK 90%).

She was admitted in our Department in May 2005 with pallor, fatigue, headache, dizziness, and splenomegaly at 8 cm below the costal margin, hepatomegaly at 2 cm below the costal margin.

The peripheral blood showed microcytic anemia: Hb 6.8 g/dL, Ht 21.2%, MCV 53 fL, mean corpuscular hemoglobin (MHC) 17 pg Rt 0.17%, WBC $3.76 \times 10^3/\mu\text{L}$ (band 1%, neutrophils 49%, eosinophils 4%, basophils 2%, lymphocytes 40%, monocytes 3%), Plt $900 \times 10^3/\mu\text{L}$, erythroblasts 3%, hypogranular neutrophils, anisocytosis (macrocytes and microcytes), poikilocytosis (ovalocytes, dacriocytes, schizocytes), basophilic stippling, Howell–Jolly bodies, Cabot rings.

Serum ferritin 609 $\mu\text{g/L}$, serum erythropoietin 22.2 mIU/mL, lactic dehydrogenase 254 IU/L, hemoglobin electrophoresis: Hb A1 94.9%, Hb A2 5.1%.

BM aspirate and biopsy: hypercellularity, marked erythroid hyperplasia with the predominance of basophilic and polychromatic forms, multinuclearity and macro-megaloblastic changes, 3% myeloblasts, dysgranulopoiesis (hypogranular and hypolobated neutrophils), polymorphous megakaryocytes, without fibrosis. Ringed sideroblasts increased over 15% (Figures 2–4).

Cytogenetic exam: 46,XX in 100% of metaphases.

JAK2 V617F negative.

The diagnosis was of RARS-T associated with β thalassemia.

The time from diagnosis was 108 months.

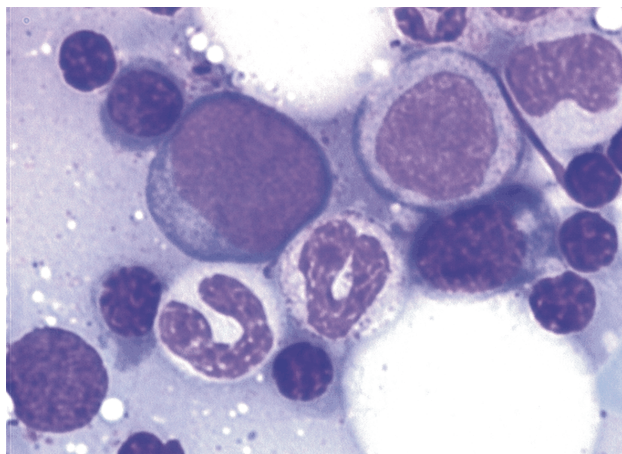


Figure 2 – Dysgranulopoiesis (hypogranular neutrophils). Bone marrow, May–Grünwald–Giemsa (MGG) staining, 100×.

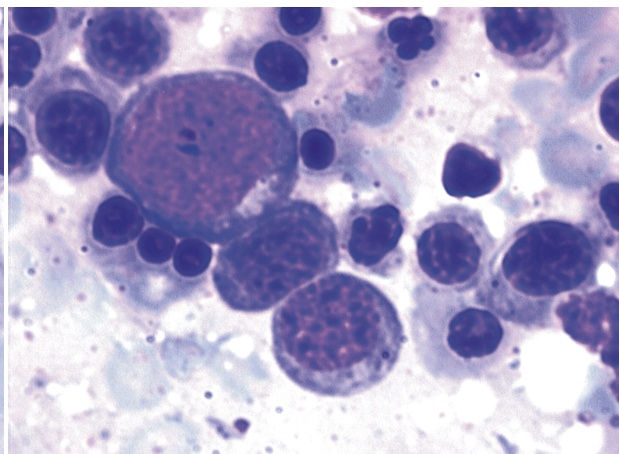


Figure 3 – Dyserythropoiesis. Bone marrow, MGG staining, 100×.

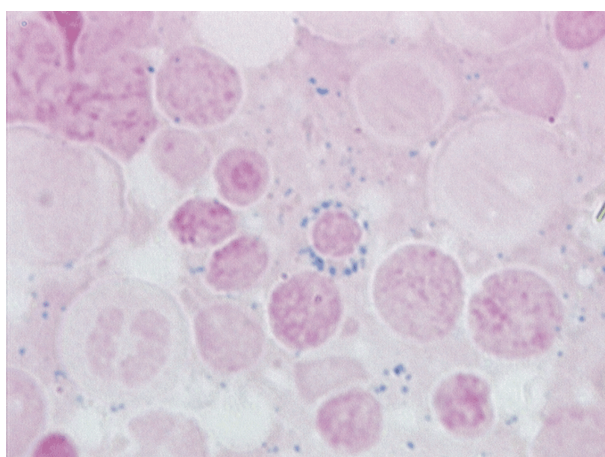


Figure 4 – Ring sideroblasts. Bone marrow, Perl's staining, 100×.

Case No. 3

The third case is an 80-year-old man patient with bilateral cataracts, hypertension, which come in our Clinic in March 2008 for the investigation of anemia and thrombocytosis.

Clinically: pallor, splenomegaly at 3 cm below the costal margin, hepatomegaly at 1 cm below the rebord. The

peripheral blood showed macrocytic anemia: Hb 10.9 g/dL, Ht 33.4%, MCV 94.6 fL, WBC $9.17 \times 10^3/\mu\text{L}$ (myelocytes 1%, bands 2%, neutrophils 69%, eosinophils 2%, basophils 1%, lymphocytes 15%, monocytes 9%), Plt $1450 \times 10^3/\mu\text{L}$, anisocytosis with macrocytosis, poikilocytosis (ovalocytes, dacriocytes, schizocytes), basophilic stippling, hyperlobated neutrophils.

Serum erythropoietin: 15.5 mIU/mL.

BM aspirate: hypercellularity, granulocytic lineage 62% with 1% myeloblasts, erythroid lineage 35%, dyserythropoiesis (megaloblastic changes, mitosis), dysplastic megakaryocytes (Figures 5–8). Ringed sideroblasts 56%. The diagnosis was compatible with MDS/MPN type RARS-T.

PBO: hypercellularity, panmyelosis, frequent erythroblasts groups normoblastic and macrocytic type, polymorphic megakaryocytes, dispersed in lax groups around vessels, lack of myelofibrosis.

Cytogenetic exam: 46,XY in 100% of metaphases.

JAK2 V617F negative.

The patient received treatment with Hydrea and anti-antiaggregant agent (Aspenter).

The time from diagnosis was 92 months.

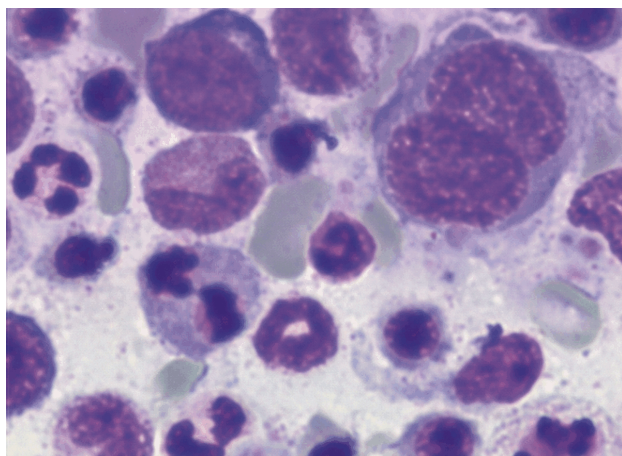


Figure 5 – Dyserythropoiesis. Bone marrow, MGG staining, 100×.

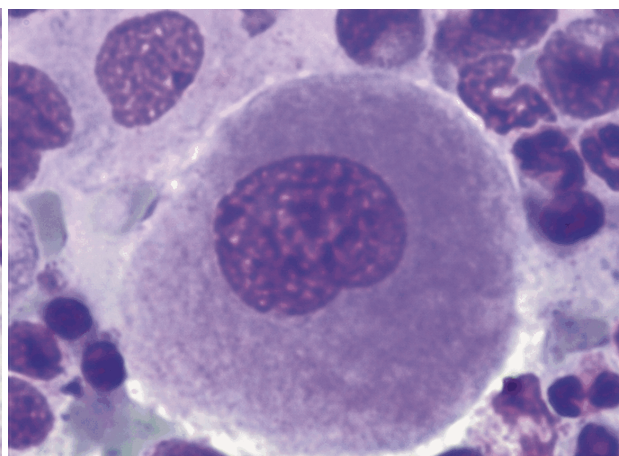


Figure 6 – Dysmegakaryopoiesis. Bone marrow, MGG staining, 100×.

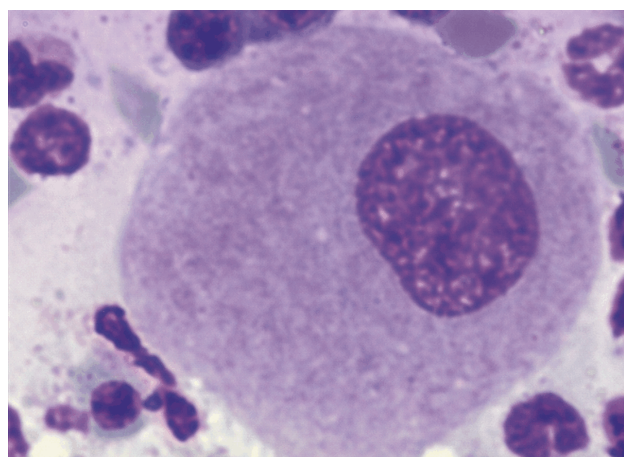


Figure 7 – Dysmegakaryopoiesis. Bone marrow, MGG staining, 100×.

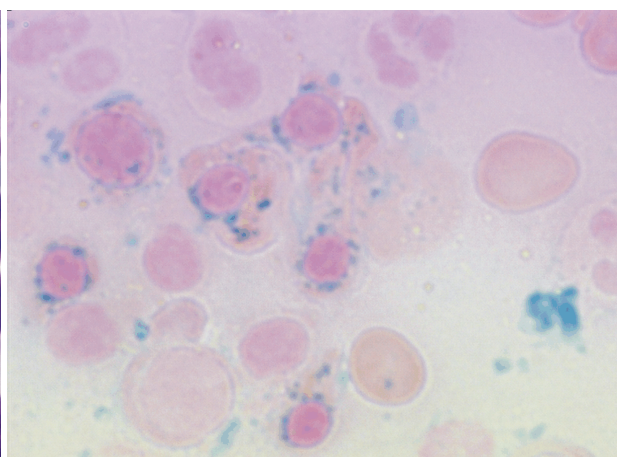


Figure 8 – Ring sideroblasts. Bone marrow, Perls' staining, 100×.

Discussion

The group was composed of two women and a man with a median age of 45.6 years (23–80-year-old). The lot features are presented in Table 1. All patients showed anemia at the diagnosis. Percentage of bone

marrow blasts was below 5%, percentage of ringed sideroblasts was over 15%, and silver stained for reticulin fibrosis was negative in all cases. JAK2 V617F mutation was absent in all cases.

Table 1 – Clinical variables of patients

Age [years]/ Gender	Hb [g/dL]	MCV [fL]	N [$\times 10^9/\mu\text{L}$]	M [$\times 10^9/\mu\text{L}$]	P [$\times 10^9/\mu\text{L}$]	BM (aspirate and biopsy) C [% blasts] Fibrosis	Dysplastic changes of myeloid lineages	RS	Cytogenetic exam	IPSS/IPSS-R	S	JAK2	Survival [months]	Treatment
23/F	6.7	130	2.346	0.168	657	Hyper-cellular 1% Fibrosis absent	Dyserythropoiesis Dysgranulopoiesis Megakaryocytic dysplasia (large multinucleate MK, micromegakaryocytes)	>15%	47,XX, +8 100% meta-phases FISH del(5q) negative	0.5/3.5	Absent	JAK2 negative BCR-ABL negative	32 Alive	Anticoagulant treatment Aspenter Red cells transfusions ESA Anagrelidum
34/F	6.8	53	1.84	0.112	900	Hyper-cellular 3% Fibrosis absent	Dyserythropoiesis Dysgranulopoiesis Polymorphic MK	>15%	46,XX 100% meta-phases	0/3	+ 10 cm	JAK2 negative BCR-ABL negative	108 Alive	Hydrea Interferon Red cells transfusions Aspenter In present: ESA, Anagrelidum
80/M	10.9	94.6	6.327	0.917	1350	Hyper-cellular 1% Fibrosis absent	Dyserythropoiesis Dysgranulopoiesis Polymorphic MK	56%	46,XY 100% meta-phases	0/0.5	+ 2 cm	JAK2 negative BCR-ABL negative	58 Alive	Hydrea Aspenter

Hb – Hemoglobin; MCV – Mean corpuscular volume; N – Neutrophils; M – Monocytes; P – Platelets; C – Cellularity; BM – Bone marrow; RS – Ringed sideroblasts; IPSS – International Prognostic Scoring System; IPSS-R – International Prognostic Scoring System-Revised; S – Splenomegaly; MK – Megakaryocytes; FISH – Fluorescent *In Situ* Hybridization.

In one study, Szpurka H *et al.* described JAK2 mutation in six patients from nine with RARS-T (67%) and three of the 26 (12%) patients with other forms of MDS/MPN, U [15]. It was observed a predominance of the male sex (M/F=12/4), the patients showed more pronounced anemia than essential thrombocythemia (ET), but were less anemia and neutropenia than other subgroups of MDS.

Steensma DP *et al.* [13] describes a frequency of JAK2 mutation in MDS 5% (3/119) and 3% (95/101) in CMML. Ohyashiki K *et al.* describes also this mutation JAK2 V617F with low frequency in MDS [16].

In our study, the cytogenetic exam described trisomy 8 chromosome in one case and karyotype was normal in two cases. In the first case, the cytogenetic risk was intermediate and good in two other cases.

Trisomy of chromosome 8 is found at 13% of patients with MDS.

Trisomy 8 is the third anomaly as common in MDS and Aul C *et al.* describe it in 11% of cases of MDS as a unique anomaly [17] and a higher incidence in males. This anomaly is associated with intermediate risk and the patients treated with hypomethylant 5-Azacytidine agents have a better survival [18, 19].

Haase D *et al.* describe trisomy 8 at 3.8% of cases of MDS and it is associated with a median survival of 23 months [20].

In most cases, cytogenetic described in the literature have shown normal karyotype. Some cytogenetic abnormalities have been described: +8, del(13q), del(20q).

These abnormalities were found in both MDS and the CMPN. Wang SA *et al.* [11] on a group of 16 patients with RARS-T described karyotype normal in 11 patients and chromosomal abnormalities in five patients (two patients with +8, one with del(7q)(q12q21) and two with complex karyotype containing del(5q). Renneville A *et al.* describe seven cases of RARS-T: six cases with normal karyotype and one case with del(11q) [21].

According with *International Prognostic Scoring System* (IPSS, 1997) and *Revised IPSS* (R-IPSS, 2012) the first patient of our study is in an intermediate score system (IPSS 0.5 and R-IPSS 3.5). Median survival under IPPS is 3.5 years and 3 years according R-IPPS. In the second case, the IPSS is 0 – low risk (median survival of 5.7 years) and IPSS-R 3 – low (median survival of 5.3 years). The third case is associated with IPPS 0 – low and IPPS-R 0.5 – very low risk (median survival of 8.8 years).

Shaw GR [22] shows a similar median survival for RARS-T and RARS, 71 months *versus* 64 months. This survival is lower than ET.

Clinically, in the first two cases of our study, patients become transfusion dependent shortly after the diagnosis, which show similarity with MDS. In these first two cases were administered erythropoiesis stimulating agents (ESA). In the first case, it was observed an increase of platelets number over $1000 \times 10^3/\mu\text{L}$, which required stopping ESA and administration of Anagrelidum. Increase of serum ferritin over 1000 ng/mL, due to the transfusions need iron chelation therapy. In the second case, ESA treatment eliminated transfusion requirements and the patient is with a good clinical status, without transfusion needing since 2007. Thrombocytosis was treated initially with Hydrea and IFN, then with Anagrelidum. In the third case, therapeutic option was Hydrea, which caused hematological improvement, without thrombotic events, improvement of anemia, transfusion independency (Hb 11 g/dL, well tolerated). All cases received antiaggregant treatment. There were thrombotic events in no cases. The period of investigation was between 32 and 108 months (Table 1). All patients are alive. A case described in literature in an old patient was treated with Hydrea and this treatment did not worsen anemia [23].

☐ Conclusions

In these three cases, the patients presented dysplastic features on two lines in two cases and three lines in one case. Although the first two cases had marked thrombocytosis, but under $1000 \times 10^3/\mu\text{L}$, however clinical evolutions were similar to that of a myelodysplastic syndrome (transfusion dependent anemia with response to the administration ESA). In the third case, because of the large number of platelets and the age of the patient was chosen Hydrea (Hydroxyurea). The treatment improved anemia in time. RARS-T remains a provisional entity; it is not understood yet if it is a single entity or there are two different pathological conditions arising simultaneously (RARS and ET). The investigation of these patients must be complex for a correct diagnosis. We believe that the therapeutic options must be individualized for each case,

depending on its special particularities, because there is not yet a standard treatment for these patients. We have not investigated SF3B1 mutation. This mutation is common in most forms of MDS with RS and is not common in the MPN.

Acknowledgments

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