research paper

haematologica 2002; 87:392-399
http://www.haematologica.ws/2002_04/392.htm

Essential thrombocythemia with ringed sideroblasts: a heterogeneous spectrum of diseases, but not a distinct entity

Annette Schmitt-Graeff, Juergen Thiele,* Irina Zuk, Hans Michael Kvasnicka*
Institutes of Pathology, Universities of Freiburg and *Cologne, Germany

Correspondence: Juergen Thiele, M.D., Institute of Pathology, University of Cologne, Joseph-Stelzmann-Str. 9, D-50924 Cologne, Germany. Phone: international +49.0221.4785008. Fax: international: +49.0221.4786360. E-mail: j.thiele@uni-koeln.de

Background and Objectives. According to the recently published WHO-classification essential thrombocythemia with ringed sideroblasts (ET/RS) remains an ambiguous category which may be considered as myelodysplastic/myeloproliferative disease, unclassifiable. Because until now only case reports or very small series of patients have been described, a more systematically performed study is warranted.

Design and Methods. A retrospective evaluation was carried out on 38 patients with the diagnosis of ET/RS and more than 15 % ringed sideroblasts on smears. Simultaneously performed bone marrow biopsies, follow-up examinations and survival data were also available.

Results. Based on cytological features and particular bone marrow findings including immunohistochemistry three patterns could be determined. These were associated with different clinical features and in particular prognosis. Group I included six patients whose diagnosis was consistent with ET, group II comprised 21 patients revealing prefibrotic and early fibrotic chronic idiopathic myelofibrosis (CIMF) and finally 11 patients (group III) displayed myelodysplastic syndromes (MDS). Follow-up studies revealed that no patient with ET showed a fiber increase but eight CIMF patients developed overt myelofibrosis and four patients of the MDS group developed secondary acute myeloid leukemia. In comparison with a control group of 39 patients with *true* ET, prognosis was significantly different because our cohort showed a median survival of 100 months that contrasted significantly with the 170 months in the patients with *true ET*.

Interpretation and Conclusions. Ringed sideroblasts are not a pathognomonic feature of MDS, but may indicate a dysplasia probably associated with a primary or secondary disturbance of iron metabolism in a variety of disorders. For this reason, a more accurate classification of so-called ET/RS patients is warranted by evaluation of smears and in particular bone marrow biopsy specimens. According to our findings these patients should be classified as having either ET, CIMF or MDS and show a significantly different survival pattern.

Key words: essential thrombocythemia, ringed sideroblasts, early myelofibrosis, myelodysplastic syndrome, marrow histology, survival.

The abnormality of ringed sideroblasts (RS) with typical perinuclear coarsely granulated (mitochondrial) iron deposits in more than 15% of the erythroid precursors has been recognized in a variety of hereditary and idiopathic acquired anemias. Refractory anemia with ringed sideroblasts (RARS) is generally considered as a clonal expansion of hematopoietic progenitor cells in the context of a myelodysplastic syndrome (MDS). Moreover, RS may occur in any other type of MDS and also in acute myeloid leukemia (AML).[1,2] While the MDS types of RS are generally associated with normal or decreased platelet counts, uncommonly a marked thrombocytosis is a leading laboratory finding in patients yielding RS in the bone marrow (BM). The significance of this peculiar association between thrombocytosis and the RS abnormality remains a matter of controversy. The association has rarely been described in patients with the *5q-syndrome*[3-6] or with conspicuous rearrangements of chromosome 3 involving band 3q21 and 3q26.[7] The latter anomaly is also seen in AML or in subtypes of MDS with a high incidence of secondary AML.[8,9] Both cytogenetic defects are accompanied by striking megakaryocytic dysplasia with a predominance of hypolobated microforms.[9] On the other hand, the occurrence of enlarged hyperlobulated megakaryocytes has been described as a characteristic

feature seen in most cases of RS with an elevated platelet count.[10] The latter cases present with a rather indolent disorder lacking any characteristic cytogenetic abnormalities including a del(5q). Therefore, the combination of thrombocytosis and RS has been repeatedly referred to as a chronic myeloproliferative disease (MPD), i.e. so-called *essential thrombocythemia with ringed sideroblasts* (ET/RS) or as mixed or overlapping myelodysplastic/myeloproliferative syndrome.[11-13] The new WHO classification recognizes the obvious difficulty of a proper classification of this unusual condition. For this reason, it is mentioned in the paragraph on ET[14] as a provisionally related entity with the explicit comment that this condition is probably best considered as a *myelodysplastic/myeloproliferative disease, unclassifiable*.[15] However, in view of the significant biological impact of a MPD of ET-type and a MDS, a clear-cut designation is very important and certainly provides useful prognostic information and also indicates different therapeutic approaches in individual patients.

This diagnostic inconsistency prompted us to evaluate morphologic, clinical and laboratory features in a series of 38 patients presenting with so-called ET/RS. Since the differentiation of initially unclassifiable MPD or MDS may be significantly advanced by follow-up studies, we carefully examined all available sequential BM trephines, follow-up and survival data until further studies determined the most appropriate category for such cases. The present investigation provides persuasive evidence that ET/RS represents not a single disease entity with overlapping MDS/MPD features, but rather a heterogeneous spectrum of conditions characterized by differences in morphology, clinical findings and, in particular, prognosis.

Design and Methods

Selection of patients

Following a scrutinized survey of hematopathological files (smears of BM aspirates and BM trephine biopsies) for all patients with a presumptive diagnosis of ET between 1988 and 2000 we identified 38 patients (17 males, 21 females; median age 72 years, range 54-86 years) with more than 15% ringed sideroblasts and a platelet count exceeding 500×10^9/L. Although this platelet level does not explicitly conform with the WHO-criteria (>600×10^9/L),[14] this slightly lower limit was selected in accordance with recent findings in a number of patients presenting with initial stage ET. [16,17]

These patients represented 2.7% of all ET cases documented during that period. The laboratory data, including age, sex, peripheral blood cell count and spleen size were derived from the corresponding clinical records. Complete information concerning follow-ups, survival data and cytogenetics could be obtained for each patient. The observation time ranged between 3 to 157 months (mean 81.5±53.0 months). Moreover, as a control group we recruited 39 patients presenting with clear-cut findings of *true* ET according to the WHO classification.[14]

Tissue specimens

All patients had representative (pretreatment) trephine biopsies and BM smears readily available for re-evaluation. Sequential BM examinations were performed with two biopsies in ten patients and three sequential biopsies in six patients. The BM specimens were fixed in an aldehyde solution for 12 to 48h (2 mL 25% glutaraldehyde, 3 mL 37% formaldehyde, 1.58 g anhydrous calcium acetate, and distilled water per 100 mL) and decalcified for 3 days in 10% buffered ethylene-diamine tetraacetic acid (EDTA), pH 7.2 as previously described.[18] Paraffin-embedded tissue sections cut at 4 μ were routinely stained with Giemsa, periodic-acid Schiff (PAS), naphthol-AS-D-chloroacetate esterase, Perls' reaction for iron and silver impregnation according to Gomori. Smears were stained with May-Grünwald Giemsa, peroxidase and Perls' reaction for iron. Immunohistochemistry was performed using the alkaline phosphatase anti-alkaline phosphatase (APAAP) method.[19] Sections were evaluated for the expression of several antigens including CD61 (anti-platelet glycoprotein IIIa),[20] myeloperoxidase, glycophorin C (Ret40f)[20] and CD34 (hematopoietic progenitors, endothelial cells).[21] Monoclonal antibodies and other reagents were purchased from Dako-Diagnostica GmbH (Hamburg, Germany) and techniques were applied as detailed previously.[18-21]

Diagnostic re-evaluation

The three hematopathologists reviewed all cases in an independent and blind fashion using the criteria of the *Polycythemia Vera Study Group*[22] and the current WHO classification[2,14,23] as well as relevant reports concerning the differential diagnosis of thrombocythemias.[24-28] Both histologic and cytological features and laboratory and clinical follow-up data were equally considered to classify each case in accordance with the different categories of MPDs or MDS. Having completed this classification a panel meeting revealed strikingly homogeneous results of classification with a negligible interobserver disagreement between the hematopathologists that was easily resolved so that a consensus was reached.

Statistical analysis

Estimates of survival were evaluated from the date of BM biopsy diagnosis before therapy to the date of death or last follow-up. Observed survival rates were calculated with the Kaplan-Meier product-limit method and differences in median survival were tested with the log-rank test. Survival data of the ET/RS patients were further compared with those previously calculated for 39 patients with well-documented ET[14] without RS.

Results

Clinical features

The clinical and hematologic data are listed in Table 1. Briefly, all patients presented with a thrombocythemic disorder that was associated with slight to pronounced anemia in the majority (33 of 38) of cases. The white blood cell counts varied from leukopenia to overt leukocytosis. There was no evidence of a Philadelphia chromosome, a BCR/ABL fusion gene or a 5q- syndrome. One patient was found to have a t(3;3)(q21;q26) anomaly. Splenomegaly was present in seven cases at initial diagnosis and developed in 15 other patients during the follow-up period. Moreover, during the observation period leukocytosis changed to leukopenia and gross anemia in seven patients. The survival characteristics of our series are shown in Figure 2. The 38 patients had a median (observed) survival of 100 months which was significantly shorter than the median survival of 170 months for a control group of 39 patients with typical ET.

Morphologic features

Overall cellularity of the BM ranged from hypo- to normo- and hypercellular. A feature common to all the smears was the presence of more than 15% ringed sideroblasts, which was a criterion for entry into this study (Figure 1a-c). Cytological features of late erythroblasts ranged from pure macrocytosis to overt dysplasia with abnormal nuclear lobulation and nuclear bridging. An increase in megakaryocytes was documented in all cases, however, with a remarkable variety of histologic and cytological features that were particularly evident by applying PAS staining and CD61 immunohistochemistry. Three different patterns of megakaryocyte morphology could be detected: group I patients (n=6) showed diffusely scattered large to giant megakaryocytes that were occasionally also arranged in loose clusters. Their nuclei displayed staghorn-like features and a broad rim of well-developed mature cytoplasm (Figure 1d,e). In these patients, there was no evidence of an increase or immaturity of the granulocytic series. Group II patients (n=21) showed, in addition to a granulocyte proliferation, a striking expression of megakaryocytic abnormalities characterized by the presence of large and dense clusters (Figure 1f,g). These contained both small immature megakaryocytes and large bizarre cells with irregular nuclear lobulation, hyperchromasia and often a cloud-like aspect (Figure 1g). $CD34^+$ progenitors and promyelocytes were not significantly increased in group I and II patients. Finally group III patients (n=11) exhibited an increase in small-sized immature megakaryocytes (Figure 1h), which were especially detected by CD61 immunolabeling (Figure 1i). These dysplastic micromegakaryocytes with abnormally lobulated or hypolobulated nuclei were often arranged in small and loose clusters (Figure 1i). Granulopoiesis ranged from hypo- to hyperplastic with various degrees of dysplasia including nuclear hypolobulation and hypogranularity. At presentation, the $CD34^+$ blast cell count in the bone marrow was more than 5% in two patients (RAEB-1) and 19% in one other case.

Evaluation of the silver impregnation stain revealed a normal reticulin content in the initial and follow-biopsies of group I patients (Figure 1e). In group II, no or a minimal focal increase of reticulin fibers was noted in 13 patients. Six patients showed an early fibrotic stage with slight reticulin

Table 1. Initial findings in patients with so-called ET/RS and corresponding data according to the retrospectively performed histologic classification.

	Total	*ET*	*CIMF*	*MDS*
No. of patients	38	6	21	11
Age (years)	72±8 (54-86)	73±5 (62-79)	73±9 (54-86)	70±8 (61-83)
Gender (F/M)	21/17	5 /1	10 /11	6 /5
Hemoglobin (g/dL)				
females	9.8±1.9 (6.0-13.0)	10.2±1.5 (8.6-11.6)	10.2±1.8 (6.7-14.6)	8.8±2.1 (6.0-11.3)
males	11.0±2.3 (6.7-14.6)	14.6 –	11.4±1.8 (8.7-14.1)	9.6 ±2.4 (6.7-12.4)
MCV (μm^3)	95±10 (76-127)	84±7 (76-92)	98±9 (84-115)	104±13 (89-127)
Thrombocytes ($\times 10^9$/L)	956±375 (533-2,115)	918±252 (533-1,290)	1,052±411 (569-2,115)	794±318 (557-1,516)
Leukocytes ($\times 10^9$/L)	10.7±5.9 (3.6-34)	8.8±2.0 (6.1-12.1)	11.4±5.1 (3.8-25.2)	10.4±8.5 (3.6-34)
Spleen size (cm)*	0.7±1.9 (0-9)	0.3±0.5 (0 -1)	1.2±2.5 (0-9)	0.1±0.6 (0-2)

**Below costal margin.*

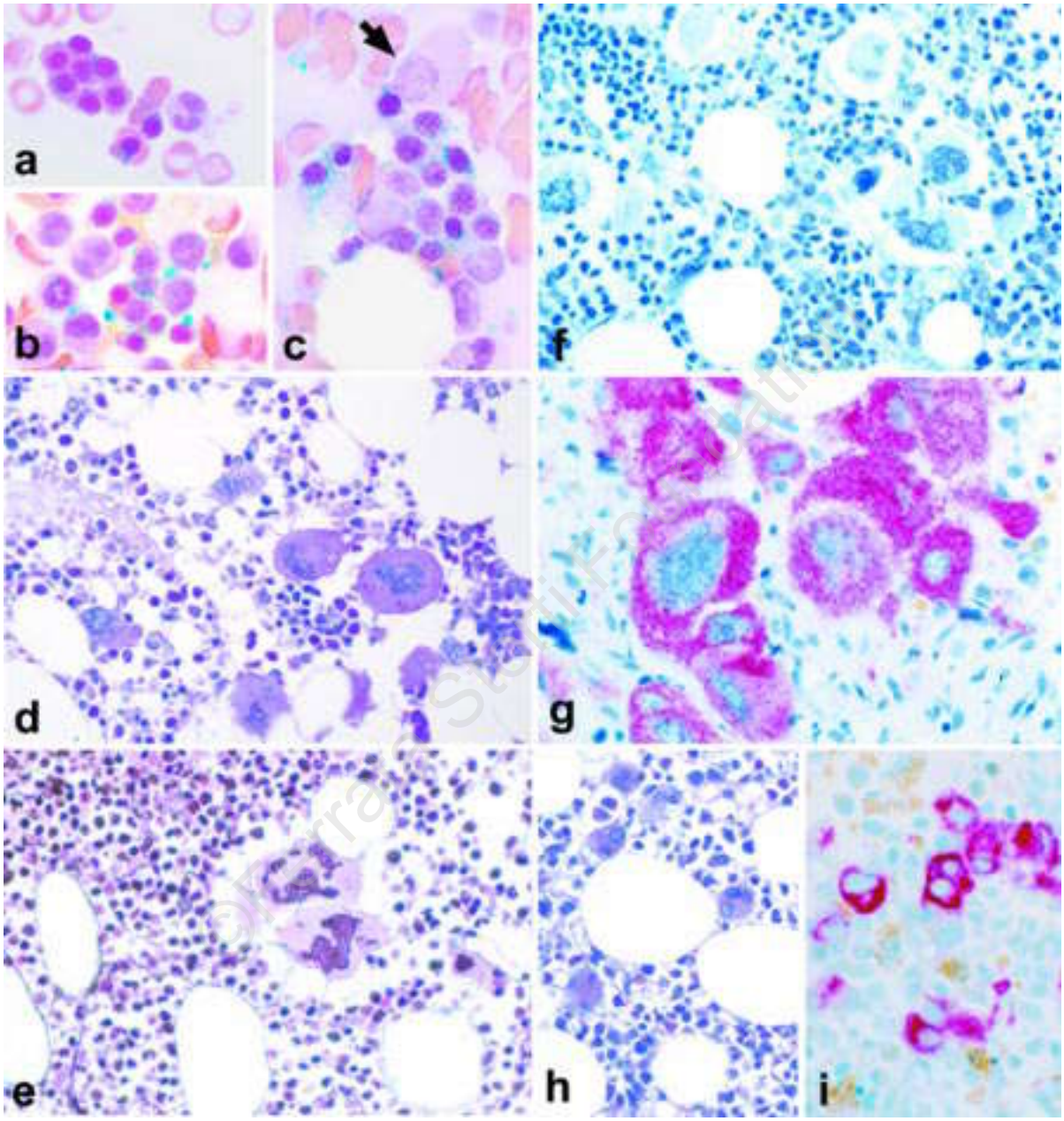

Figure 1. a-i. Smears of aspirates (a-c) and bone marrow sections (d-e). Smears show ringed sideroblasts in *true* ET (a), CIMF (b) and MDS (c) with an atypical micromegakaryocyte (arrow). (d) Histologic sections of *true* ET with large to giant megakaryocytes revealing very loose clusters and deeply lobulated (staghorn-like) nuclei without fiber increase in the marrow (e). (f) shows CIMF showing dense cluster of abnormal megakaryocytes with hypolobulated, bulbous (cloud-like) nuclei that are easily demonstrable after immunostaining (g). h MDS exhibits tiny clusters of dysplastic micromegakaryocytes some of them with atypical or hypolobulated small nuclei (i). (a-c). Perls' reaction, (d) and (h) PAS reaction, (e) silver impregnation (Gomori's technique), (f) Giemsa, (g) and (i) CD61-immunostaining. (a-c) and (g) ×570, (d-f) and (h) and (i) ×350.

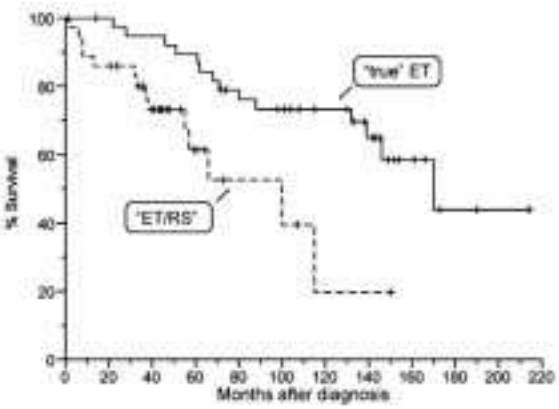

Figure 2. Survival in so-called ET/RS (38 patients) compared to in *true* ET (39 patients). There is a significant difference between these two cohorts ($p = 0.0030$).

fibrosis, but without collagen deposits (fibrosis grade 1+) and two patients exhibited moderate reticulin fibrosis (grade 2+). Follow-up biopsies were available for eight out of 21 patients in this group. Here a transition from a prefibrotic stage to grade 1+ and 2+ fibrosis was documented in five patients and marked fibrosis with associated osteosclerosis (grade 3+) in another two patients. The development of overt fibrosis was accompanied by splenomegaly and obvious abnormalities of peripheral blood cells including a leuko-erythroblastic picture and presence of dacryocytes (teardrop cells). In group III patients, no or a slight focal condensation of reticulin fibers was observed. However, in follow-up biopsies, unlike the changes in group II, no progression to an advanced fibrotic stage occurred.

Finally, we compared the morphologic and clinical features observed in these cases of so-called ET/RS with corresponding disease entities defined by the new WHO classification.[1,2,14,23] This approach allowed us to recognize three distinctive entities within the spectrum of ET/RS. In group I patients, bone marrow histopathology, especially megakaryocyte morphology and absence of fibrosis was consistent with ET and identical with that of our control group representing *true* ET. Accordingly in both cohorts clinical data and survival times were not significantly different with exception of the hemoglobin level (Table 1) in two female patients with a history of severe hemorrhage.[14] Group II patients clearly showed morphologic and clinical features of CIMF.[23] At initial presentation, most of the patients included in this group had prefibrotic or early fibrotic CIMF that progressed to a more advanced fibrotic stage in seven of eight follow-up biopsies. Their survival time was significantly shorter (Table 2) than that of the control series of ET patients. Morphologic and laboratory data of group III patients were generally compatible with MDS, e.g. with the categories of refractory anemia with ringed sideroblasts and refractory anemia with excess of blasts (RAEB-1 and –2).[1,2] Progression into secondary AML occurred in four of the patients, one of whom had a t(3;3)(q21;q26) anomaly. Of all the groups under consideration this cohort had the most unfavorable prognosis (Table 2).

Discussion

The current WHO classification refers to thrombocythemic disorders associated with RS in two paragraphs. First, *acquired sideroblastic anemia associated with thrombocytosis* is mentioned as a provisional entity related to ET with the explicit statement that features of both a MDS and MPD exist and further studies are warranted to determine the exact category for such cases.[14] Secondly, *refractory anemia with ringed sideroblasts (RARS) associated with marked thrombocytosis* is included in the category *myelodysplastic/myeloproliferative disease, unclassifiable (MDS/MPD, U)*.[15] The discussion of the latter paragraph focuses on the point of whether this disease represents one end of the spectrum of RARS, or the simultaneous occurrence of two separate disorders (RARS and ET). According to the definition given by the authors, the designation as MDS/MPD, U refers to the concept that the disease has clinical, laboratory and morphologic features supporting the diagnosis of both a MPD and a MDS. However, since it

Table 2. Survival characteristics for patients with so-called ET/RS according to morphologic classification and for the control group with *true* ET.

Group	*No. of. patients*	*No. of deaths*	*Median survival (months)*	*Log-rank test*
ET/RS	38	15	100	p=0.0251°
ET	6	0	*	
CIMF	21	8	98	
MDS	11	6	57	
true ET	39	14	170	p=0.0030#

*°Log-rank test for heterogeneity; #ET/RS vs. true ET; *no patient died during the observation period (3 to 157 months).*

does not meet all the criteria of any of the other entities included in the MDS/MPD category[13] it should not be placed into the group of MPD unclassifiable.[29] The results of our retrospective study provide convincing evidence that so-called ET/RS represents a heterogeneous, until now ill-defined disease that includes a wide spectrum of conditions comprising both myeloproliferative and myelodysplastic disorders in the strict sense. For this reason, we cannot agree with those authors who, based on case reports or very small series of patients, classify this disease as a mixed myeloproliferative/myelodysplastic or overlap syndrome.[11-13,15] Our findings are in keeping with the assumption that so-called ET/RS shows features characteristic of either a true MPD or of a MDS. Appropriate histologic and immunohistologic studies of trephine BM biopsies in combination with cytological, clinical and laboratory examinations enabled us to distinguish clearly three different categories, i.e. ET, CIMF and MDS. Positive criteria that allow a distinction between early prefibrotic CIMF and (true) ET have recently been established.[14,23,24,30,31] In our series, more than half of the cases could be diagnosed as early prefibrotic CIMF with progression to an overt fibrotic stage in most patients during the observation period. About one third of patients clearly showed features of MDS ranging from RARS to RAEB with transition into AML. Because CIMF and MDS were significantly associated with a poorer prognosis than *true* ET, unequivocal separation of these different entities is warranted. According to our experience concerning exact diagnostic evaluation, the histologic examination of BM biopsies proved to be extremely useful and more accurate than cytological examination alone.[18,24,30,31] On the other hand, since the definition of ringed sideroblasts is based on cytology, proper smears must be examined together with BM trephines. Mitochondrial iron deposits are easily dissolved during tissue processing and therefore determination of this feature by using biopsy specimens alone must be regarded rather critically. Morphologic parameters such as megakaryocyte size, arrangement within the marrow space (histotopography), nuclear differentiation and possible maturation defects as well as the pattern of the reticulin fiber meshwork, seem to be the most effective method for reaching an accurate classification.[14,18,23-27,30] We assume that the occurrence of RS in thrombocythemic disorders should not be considered as the pathognomonic or defining criterion of this heterogeneous spectrum of conditions. This proposition is in accordance with the WHO classification of the MDS in which the presence of more than 15% of RS alone is not considered as the relevant criterion of RARS, when multilineage dysplasia and an increased blast percentage are present.[1] Clinical studies have shown that even typical RARS comprises two prognostic forms: a favorable category with pure RARS affecting exclusively the erythroid lineage and another category with additional abnormalities of the granulocytic and megakaryocytic series indicating multilineage dysplasia and a higher risk of evolution into AML.[32,33] In the conditions presented here, the evaluation of BM trephines by hematopathologists provided key information for the clear-cut distinction between MDS or MPD categories eventually associated with RS that simulate so-called ET/RS. In this context RS are a concomitant feature which may occur due to folate acid deficiency in some patients. The appearance of RS is consistent with dysplasia (coarse mitochondrial iron deposits) that may reflect a functional primary or secondary disturbance of iron turnover comparable with that occurring in certain enzyme defects of azurophilic granules in neutrophils in MDS. Since the morphologic differences between the various groups, especially ET and CIMF[18,26,30] may be subtle at initial presentation of patients, there should be a professional work-up of specimens. Follow-up BM biopsies may provide additional information to permit a more precise designation in previously unclassifiable cases.[29]

In conclusion, the importance of an exact classification of so-called ET/RS cannot be overemphasized. When pursuing this diagnostic challenge it will become more and more evident that ET/RS is not a defined entity but a heterogenous group of different disorders that share the common finding of ringed sideroblasts and an elevation of platelet count. The assignment of individual patients to the categories of *true* ET, CIMF or MDS provides important predictive parameters for the biological course of the disease and response to therapy and may also help clinicians to define the best treatment strategies.

Contributions and Acknowledgments

ASG designed the study, reviewed the bone marrow biopsies, contributed to the interpretation of data and drafted the article. JT and HMK reviewed the bone marrow biopsies, revised the article, performed the statistical analysis and contributed substantially to the interpretation of the data. IZ was involved in the collection and interpretation of the clinical-laboratory data including follow-up examinations of patients.

Disclosures
Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

References

1. Brunning RD, Bennett JM, Flandrin G, et al. Myelodysplastic syndromes: Introduction. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 63-7.
2. Brunning RD, Bennett JM, Flandrin G, et al. Refractory anaemia with ringed sideroblasts. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 69.
3. Dewald GW, Davis MP, Pierre RV, O'Fallon JR, Hoagland HC. Clinical characteristics and prognosis of 50 patients with a myeloproliferative syndrome and deletion of part of the long arm of chromosome 5. Blood 1985; 66:189-97.
4. Mathew P, Tefferi A, Dewald GW, Goldberg SL, Su J, Hoagland HC, et al. The 5q- syndrome: a single-institution study of 43 consecutive patients. Blood 1993; 81: 1040-5.
5. Boultwood J, Lewis S, Wainscoat JS. The 5q-syndrome. Blood 1994; 84:3253-60.
6. Koike T, Uesugi Y, Toba K, Narita M, Fuse I, Takahashi M, et al. 5q-syndrome presenting as essential thrombocythemia: myelodysplastic syndrome or chronic myeloproliferative disorders? Leukemia 1995; 9:517-8.
7. Carroll AJ, Poon MC, Robinson NC, Crist WM. Sideroblastic anemia associated with thrombocytosis and a chromosome 3 abnormality. Cancer Genet Cytogenet 1986; 22:183-7.
8. Bitter MA, Neilly ME, Le Beau MM, Pearson MG, Rowley JD. Rearrangements of chromosome 3 involving bands 3q21 and 3q26 are associated with normal or elevated platelet counts in acute nonlymphocytic leukemia. Blood 1985; 66:1362-70.
9. Jotterand Bellomo M, Parlier V, Muhlematter D, Grob JP, Beris P. Three new cases of chromosome 3 rearrangement in bands q21 and q26 with abnormal thrombopoiesis bring further evidence to the existence of a 3q21q26 syndrome. Cancer Genet Cytogenet 1992; 59: 138-60.
10. Anastasi J, Vardiman JW. Chronic myelogenous leukemia and the chronic myeloproliferative disorder. In: Knowles DM, ed. Neoplastic Hematopathology. 2nd edition. Philadelphia: Lippincott Williams Wilkins; 2001. p. 1745-90.
11. Neuwirtova R, Mocikova K, Musilova J, Jelinek J, Havlicek F, Michalova K, et al. Mixed myelodysplastic and myeloproliferative syndromes. Leuk Res 1996; 20:717-26.
12. Gupta R, Abdalla SH, Bain BJ. Thrombocytosis with sideroblastic erythropoiesis: a mixed myeloproliferative myelodysplastic syndrome. Leuk Lymphoma 1999; 34: 615-9.
13. Bain BJ. The relationship between the myelodysplastic syndromes and the myeloproliferative disorders. Leuk Lymphoma. 1999; 34:443-9.
14. Imbert M, Pierre R, Thiele J, Vardiman JW, Brunning RD, Flandrin G. Essential thrombocythaemia. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001; p. 39-41.
15. Bain B, Vardiman JW, Imbert M, Pierre R. Myelodysplastic/myeloproliferative disease, unclassifiable. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 58-9.
16. Lengfelder E, Hochhaus A, Kronawitter U, Hoche D, Queisser W, Jahn-Eder M, et al. Should a platelet limit of 600×10^9/L be used as a diagnostic criterion in essential thrombocythaemia? An analysis of the natural course including early stages. Br J Haematol 1998; 100:15-23.
17. Sacchi S, Vinci G, Gugliotta L, Rupoli S, Gargantini L, Martinelli V, et al. Diagnosis of essential thrombocythemia at platelet counts between 400 and 600×10^9/L. Gruppo Italiano Malattie Mieloproliferative Croniche (GIMMC). Haematologica 2000; 85:492-5.
18. Thiele J, Kvasnicka HM, Zankovich R, Diehl V. Relevance of bone marrow features in the differential diagnosis between essential thrombocythemia and early stage idiopathic myelofibrosis. Haematologica 2000; 85:1126-34.
19. Cordell JL, Falini B, Erber WN, Ghosh AK, Abdulaziz Z, MacDonald S, et al. Immunoenzymatic labeling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP complexes). J Histochem Cytochem 1984; 32: 219-29.
20. Gatter KC, Cordell JL, Turley H, Heryet A, Kieffer N, Anstee DJ, et al. The immunohistological detection of platelets, megakaryocytes and thrombi in routinely processed specimens. Histopathology 1988; 13:257-67.
21. Soligo D, Delia D, Oriani A, Cattoretti G, Orazi A, Bertolli V, et al. Identification of $CD34^+$ cells in normal and pathological bone marrow biopsies by QBEND10 monoclonal antibody. Leukemia 1991; 5:1026-30.
22. Murphy S, Peterson P, Iland H, Laszlo J. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol 1997; 34:29-39.
23. Thiele J, Imbert M, Pierre R, Vardiman JW, Brunning RD, Flandrin G. Chronic idiopathic myelofibrosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 35-8.
24. Thiele J, Schneider G, Hoeppner B, Wienhold S, Zankovich R, Fischer R. Histomorphometry of bone marrow biopsies in chronic myeloproliferative disorders with associated thrombocytosis: features of significance for the diagnosis of primary (essential) thrombocythaemia. Virchows Arch A Pathol Anat Histopathol 1988; 413:407-17.
25. Buss DH, O'Connor ML, Woodruff RD, Richards FD, Brockschmidt JK. Bone marrow and peripheral blood findings in patients with extreme thrombocytosis. A report of 63 cases. Arch Pathol Lab Med 1991; 115:475-80.
26. Buhr T, Georgii A, Schuppan O, Amor A, Kaloutsi V. Histologic findings in bone marrow biopsies of patients with thrombocythemic cell counts. Ann Hematol 1992; 64: 286-91.
27. Michiels JJ, Juvonen E. Proposal for revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the Thrombocythemia Vera Study Group. Semin Thromb Hemost 1997; 23:339-47.
28. Jantunen R, Juvonen E, Ikkala E, Oksanen K, Anttila P,

Hormila P, et al. Essential thrombocythemia at diagnosis: causes of diagnostic evaluation and presence of positive diagnostic findings. Ann Hematol 1998; 77:101-6.
29. Thiele J, Imbert M, Pierre R, Vardiman JW, Brunning RD, Flandrin G. Chronic myeloproliferative disease, unclassifiable. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 42-4.
30. Thiele J, Kvasnicka HM, Werden C, Zankovich R, Diehl V, Fischer R. Idiopathic primary osteo-myelofibrosis: a clinico-pathological study on 208 patients with special emphasis on evolution of disease features, differentiation from essential thrombocythemia and variables of prognostic impact. Leuk Lymphoma 1996; 22:303-17.
31. Annaloro C, Lambertenghi Deliliers G, Oriani A, Pozzoli E, Lambertenghi Deliliers D, Radaelli F, et al. Prognostic significance of bone marrow biopsy in essential thrombocythemia. Haematologica 1999; 84:17-21.
32. Cazzola M, Barosi G, Gobbi PG, Invernizzi R, Riccardi A, Ascari E. Natural history of idiopathic refractory sideroblastic anemia. Blood 1988; 71:305-12.
33. Gattermann N, Aul C, Schneider W. Two types of acquired idiopathic sideroblastic anaemia (AISA). Br J Haematol 1990; 74:45-52.

PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Jerry L. Spivak, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Spivak and the Editors. Manuscript received November 27, 2001; accepted March 4, 2002.

What is already known on this topic

Although it has been reported that thrombocytosis is associated with a more favorable prognosis in idiopathic sideroblastic anemia, little is known about the significance of ringed sideroblasts in essential thrombocythemia. Indeed, in all large published series of essential thrombocythemia patients, iron deficiency was frequent and ringed sideroblasts were not described.

What this study adds

This useful study is the first to systematically analyze the clinical and laboratory features of patients meeting the diagnostic criteria for essential thrombocythemia who were also found to have ringed sideroblasts. Such patients were uncommon, comprising only 2.7% of the authors' total essential thrombocythemia population.

Potential implications for clinical practice

The authors found that so-called essential thrombocythemia with ringed sideroblasts represented a heterogenous group of disorders including myelodysplasia and idiopathic myelofibrosis as well as essential thrombocythemia. Although the number of patients was small, the presence of ringed sideroblasts with essential thrombocythemia was associated with a reduced survival when compared with essential thrombocythemia patients lacking this abnormality.

Jerry L. Spivak, Associate Editor