HEMATOLOGY

Brief report

Erythroid hypoplasia among patients with myelodysplastic neoplasms

Cecilia Anna Fidanza[1], Wilma Barcellini[2], Bruno Fattizzo[1,2]

[1]*University of Milan, Department of Oncology and Oncohematology, Milan, Italy;*
[2]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Hematology Unit, Milan, Italy*

INTRODUCTION

Historically, erythroid hypoplasia has been considered a morphologic variant of myelodysplastic neoplasms (MDS), not exceeding 1-2% of cases in the described cohorts[1-4]. About 70% of MDS patients presents with anemia and many of them become transfusion dependent. Therapeutic options in MDS associated anemia are limited, with transfusion independence and erythroid hematologic improvement ranging from 30 to 60%, depending on the study[5]. Most patients will fail available treatments, thus representing an important unmet need.

The last WHO classification mandates bone marrow trephine evaluation with special focus to fibrosis and cellularity[6]. At variance, erythroid hypoplasia might be disregarded resulting in insidious differential diagnosis with pure red cell aplasia (PRCA), a rare condition characterized by severe hypo-regenerative anemia and reduced erythroid bone marrow precursors.

MATERIALS AND METHODS

In this retrospective study, we assessed the prevalence of erythroid hypoplasia within a monocentric cohort of MDS patients, reclassified as the new WHO 2022 myeloid edition[6] with all risk categories according to R-IPSS risk score, diagnosed between 2001 and 2023 at a tertiary hematologic center in Milan, Italy, reference for immune cytopenias. Erythroid hypoplasia was evaluated on both bone marrow aspirate and trephine at diagnosis, along with clinical, hematological, molecular data, as well as treatments and outcomes. The study was conducted in accordance to the Declaration of Helsinki.

RESULTS

Among 273 patients (median age 76 years, range 41-101; male to female ratio of 1.28), 14 (5%) showed erythroid hypoplasia on bone marrow evaluation (5 on both aspirate and trephine, 8 only on aspirate with normocellular erythroid compartment at trephine and 1 on trephine with normal cytological evaluation). **Table I** shows clinical and hematological characteristics divided according to the presence/absence of erythroid hypoplasia. In both subgroups the majority of patients was classified as MDS with low blasts, the hypoplastic phenotype was significantly higher in patients with erythroid hypoplasia. Patients with erythroid hypoplasia at diagnosis had lower median Hb levels (8.5 *vs* 10 g/dL, p=0.06), higher endogenous erythropoietin values (median 474 *vs* 52 U/L,

Arrived: 21 November 2024
Accepted: 14 February 2025
Correspondence: Bruno Fattizzo
e-mail: fattizzo@unimi.it

Table I - *Clinical and hematological patient's characteristics divided according to the presence/absence of erythroid hypoplasia*

	All patients (No.=273)	Erythroid hypoplasia (No.=14)	Erythroid normo/ hyperplasia (No.=229)	p-value
Median age, years (range)	76.4 (41-101)	77 (59-84)	75.8 (41-101)	ns
Median follow-up, months (range)	39 (0-260)	12.7 (0-72.9)	37.7 (0-260)	ns
Death, No. (%)	49 (18)	2 (14.3)	32 (14)	ns
Sex: Female, No. (%)	120 (44)	6 (42.9)	102 (44.5)	ns
WHO 2022 myeloid classification				
MDS with low blasts	178 (65.2%)	8 (57.1%)	151 (66%)	ns
MDS with increased blasts	12 (4.4%)	0	10 (4.4%)	ns
MDS with increased blasts and fibrosis	3 (1.1%)	1 (7.2%)	2 (0.8%)	ns
MDS, hypoplastic	15 (5.5%)	3 (21.4%)	11 (4.8%)	**<0.05**
MDS with low blasts and isolated 5q deletion	22 (8%)	2 (14.3%)	17 (7.4%)	ns
MDS with low blasts and SF3B1 mutation	42 (15.4%)	0	37 (16.2%)	ns
MDS with biallelic TP53 inactivation	1 (0.4%)	0	1 (0.4%)	ns
R-IPSS risk score				ns
Very low, No. (%)	92 (34.5)	3 (27.3)	80 (35.2)	
Low, No. (%)	118 (44.2)	4 (36.4)	101 (44.5)	
Intermediate, No. (%)	45 (16.9)	3 (27.3)	35 (15.4)	
High, No. (%)	7 (2.6)	0	7 (3.1)	
Very high, No. (%)	5 (1.9)	1 (9)	4 (1.8)	
Laboratory values, median (range)				
Hemoglobin (g/dL)	9.9 (5.5-16.4)	8.5 (7-14.5)	10 (5.5-16.4)	**0.06**
Reticulocytes ($\times 10^9$/L)	0.051 (0.005-0.87)	0.025 (0.005-0.29)	0.052 (0.006-0.87)	ns
ANC ($\times 10^9$/L)	2,100 (210-12,120)	1,970 (440-3,890)	2,080 (210-11,650)	ns
Platelet count ($\times 10^9$/L)	136 (7-1,024)	89 (23-309)	141 (11-1,024)	ns
Endogenous erythropoietin (U/L)	49 (6-4,368)	474 (9.41-4,368)	52 (6-793)	**<0.05**
RBC-TD, No. (%)	89 (32.6)	9 (64.3)	68 (29.7)	**<0.05**
Bone marrow cellularity				
Median, % (range)	40 (10-95)	25 (10-80)	50 (10-95)	**<0.05**
Normocellular, No. (%)	92 (36.1)	3 (23)	81 (35.7)	
Hypercellular, No. (%)	131 (51.4)	5 (38.5)	121 (53.3)	
Hypocellular, No. (%)	32 (12.5)	5 (38.5)	25 (11)	
Erythroid hypoplasia: yes, No. (%)	14 (5.7)	14 (100)	0	**<0.05**
Bone marrow lymphoid infiltrate				ns
T, No. (%)	186 (68.1)	11 (84.6)	175 (81.6)	
B, No. (%)	0	0	0	
Mixed, No. (%)	34 (12.5)	2 (15.4)	38 (18.4)	
Bone marrow fibrosis				ns
MF-1 or more, No. (%)	64 (25.6)	6 (46.2)	55 (24.2)	
NGS, No. (%)	140 (51.3)	10 (71.4)	125 (58.6)	ns
Mutations, No. (%)	95 (67.9)	4 (40)	88 (70.4)	**<0.05**
Cytogenetics, No. (%)	272 (99.6)	14 (100)	229 (100)	ns
Abnormal, No. (%)	80 (29.40)	4 (28.6)	67 (29.2)	
Rhepo, No. (%) Response: yes, No. (%)	104 (38.1) 94 (67.6)	8 (57.1) 6 (75)	82 (35.8) 50 (65)	ns ns

Continues on next page

Table I - *Clinical and hematological patient's characteristics divided according to the presence/absence of erythroid hypoplasia (continued from previous page)*

	All patients (No.=273)	Erythroid hypoplasia (No.=14)	Erythroid normo/ hyperplasia (No.=229)	p-value
Hematologic treatment, other than Rhepo				
Cyclosporine + Steroids, No. (%) Response: yes, No. (%)	7 (2.6) 6 (85.7)	4 (28.6) 4 (100)	3 (1.3) 2 (66.7)	**<0.05** ns
Eltrombopag, No. (%) Response: yes, No. (%)	23 (8.4) 16 (69.6)	2 (14.3) 1 (50)	21 (9.2) 15 (71.4)	ns
Lenalidomide, No. (%) Response: yes, No. (%)	8 (2.9) 5 (62.5)	2 (14.3) 0	6 (2.6) 5 (83.4)	ns
Luspatercept, No. (%) Response: yes, No. (%)	20 (7.3) 10 (50)	0	20 (8.7) 10 (50)	ns
Danazol, No. (%) Response: yes, No. (%)	6 (2.2) 2 (33.4)	0	6 (2.6) 2 (33.4)	ns
Steroids monotherapy, No. (%) Response: yes, No. (%)	37 (13.6) 14 (37.8)	2 (14.3) 0	35 (15.3) 14 (40)	ns

ns: not significant.

p<0.05) and a greater red blood cell (RBC) transfusion burden (64.3 *vs* 29.7%, p<0.05). Moreover, this group had lower median platelets levels (89 *vs* 141×10^9/L), although not significantly, and showed lower total cellularity (25 *vs* 50%, p<0.05). Other known causes of anemia such as vitamin or sideral deficiency, drug induced anemia, Parvovirus infection or hemolysis were routinely excluded in all patients at diagnosis. The degree of dysplasia, lymphoid infiltrate, reticulin fibrosis, and cytogenetics were largely comparable between the two groups. Next generation sequencing (NGS) analysis for genes associated with myeloid neoplasms showed a lower prevalence of genomic alterations in patients with erythroid hypoplasia *vs* the others (40 *vs* 70%, p<0.05). Mutations detected in the former involved ASXL1, DNMT3A, RUNX1, TP53, U2AF1, and PHF6 genes. Treatment with erythropoiesis stimulating agents (ESAs), as recombinant erythropoietin (Rhepo), had similar outcomes in both subgroups (about 70% response rate), but the median duration of response was significantly shorter in patients with erythroid hypoplasia (median 673 *vs* 759 days, p<0.05). The latter received more frequently treatment with cyclosporin (CyA) (28.6 *vs* 1.3%, p<0.05), always in combination with steroids then tapered until suspension, and had a better response to it (100 *vs* 66.7%), although not significantly; the median time to response to CyA was 44 days (range 15-180) in the entire cohort.

Other treatments included corticosteroids alone, thrombopoietin receptor agonists, and lenalidomide due to del(5q), they were comparable within patients with and without erythroid hypoplasia and yielded responses similar to those reported in the literature (**Table I**). Luspatercept and danazol were used only in MDS patients without erythroid hypoplasia.

DISCUSSION

Our data show that erythroid hypoplasia is present in more than 5% of MDS patients and is often disregarded. Hypoplastic patients showed more severe transfusion dependent anemia, higher levels of endogenous erythropoietin, and shorter duration of response to ESAs. Moreover, hypoplastic patients were more frequently treated with CyA and had fairly higher response rates than other MDS population. This finding highlights the importance of considering the morphological characteristics of the erythroid compartment that may give hints to an immunomodulating therapeutical approach, similar to PRCA[7]. Additionally, no response to steroids as single agent was observed in hypoplastic patients, suggesting its early association with CyA in this setting.

The lower responses to Rhepo and lenalidomide observed in hypoplastic patients further highlights that these patients with erythroid hypoplasia deserve a specific approach different from general MDS.

The differential diagnosis between MDS with erythroid hypoplasia and PRCA may be challenging. In an attempt to classify PRCA, Robert T. Means Jr distinguished a "primary myelodysplastic PRCA", an acquired clonal disorder characterized by primary pure red cell aplasia and multilineage dysplasia, from a "primary autoimmune PRCA", where humoral/cellular autoimmunity played a major role[8,9]. Additionally, several "secondary" forms of PRCA were described, linked to various autoimmune/inflammatory conditions, infections such as Parvovirus B19, neoplastic disorders, or certain drugs[10]. The patients described in our study might be those of the first category, given the presence of somatic mutations of myeloid genes, and the detection of bone marrow dysplasia, along with an older age. Nonetheless, a portion of erythroid hypoplastic patients do not present molecular (60%) or cytogenetic abnormalities (71.4%), highlighting a subset of patients with non-clonal erythroid hypoplasia and morphological aspects of dysplasia, worthy of monitoring over time.

No patient evolved to acute myeloid leukemia, consistently with previous reports of <1% risk of leukemic transformation[8].

CONCLUSIONS

This study highlights a non-negligible prevalence of erythroid hypoplasia among patients diagnosed with MDS, advising the critical evaluation of morphological bone marrow findings to inform treatment with immunosuppressive agents. A more in-depth molecular analysis may reveal in the future whether certain subtypes of MDS are more prone to develop erythroid hypoplasia due to intrinsic abnormalities in erythroid progenitor cells, rather than due to an immune-mediated attack, resembling the previously mentioned primary myelodysplastic PRCA.

ETHICAL CONSIDERATION

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each participant/patient for study participation and data publication.

FUNDING

This study was funded by Italian Ministry of Health - Current research IRCCS.

AUTHORS' CONTRIBUTIONS

All Authors followed the patients. CAF and FB conceived and wrote the paper. CAF collected the data. WB critically reviewed the manuscript. All Authors approved the final version of the manuscript.

The Authors declare no conflicts of interest.

REFERENCES

1. Wang H, Niu H, Zhang T, Xing L, Shao Z, Fu R. Low- and intermediate-risk myelodysplastic syndrome with pure red cell aplasia. Hematology. 2021; 26(1): 444–446. doi: 10.1080/16078454.2021.1929694
2. García-Suárez J, Pascual T, Muñoz MA, Herrero B, Pardo A. Myelodysplastic syndrome with erythroid hypoplasia/aplasia: a case report and review of the literature. Am J Hematol. 1998; 58(4): 319-325. doi: 10.1002/(sici)1096-8652(199808)58:4<319::aid-ajh12>3.0.co;2-2.
3. Goyal R, Varma N, Marwaha RK. Myelodysplastic syndrome with erythroid hypoplasia. J Clin Pathol. 2005; 58(3): 320-321. doi: 10.1136/jcp.2004.020974.
4. Cerchione C, Catalano L, Cerciello G, Avilia S, Picardi M, Risitano AM, et al. Role of lenalidomide in the management of myelodysplastic syndromes with del(5q) associated with pure red cell aplasia (PRCA). Ann Hematol. 2015; 94(3): 531-534. doi: 10.1007/s00277-014-2192-z.
5. Lewis R, Bewersdorf JP, Zeidan AM. Clinical management of anemia in patients with myelodysplastic syndromes: an update on emerging therapeutic options. Cancer Manag Res. 2021; 13: 645-657. doi: 10.2147/CMAR.S240600.
6. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022; 36(7): 1703-1719. doi: 10.1038/s41375-022-01613-1.
7. Hirokawa M, Sawada K, Fujishima N, Teramura M, Bessho M, Dan K, et al; PRCA Collaborative Study Group. Long-term outcome of patients with acquired chronic pure red cell aplasia (PRCA) following immunosuppressive therapy: a final report of the nationwide cohort study in 2004/2006 by the Japan PRCA collaborative study group. Br J Haematol. 2015; 169(6): 879-886. doi: 10.1111/bjh.13376.
8. Means RT Jr. Pure red cell aplasia. Blood. 2016; 128(21): 2504-2509. doi: 10.1182/blood-2016-05-717140.
9. Means RT Jr. Pure red cell aplasia: the second hundred years. Am J Med Sci. 2023; 366(3): 160-166. doi: 10.1016/j.amjms.2023.06.009.
10. Means RT Jr. Pure red cell aplasia. Hematology Am Soc Hematol Educ Program. 2016; 2016(1): 51-56. doi: 10.1182/asheducation-2016.1.51.