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Original Article

Clinicopathological associations of acquired erythroblastopenia

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Abstract: Introduction: Acquired erythroblastopenia (AE) is a rare clinical situation. It is characterized by the reduction of erythroid precursors in the bone marrow together with the low reticulocyte counts in the peripheral blood. Background: Main secondary causes of AE are drugs, Parvovirus B19 and other infectious reasons, lymphoid and myeloid neoplasia, autoimmune diseases, thymoma and pregnancy. The aim of this study is to assess the frequencies and clinical associations of AE via analyzing 12340 bone marrow samples in a retrospective manner. Material and method: Bone marrow aspirations which were obtained from patients who applied to Hacettepe University Hematology Clinic between 2002 and 2013, were analyzed retrospectively. Results: Thirty four erythroblastopenia cases were found. Patients ranged in age from 16 to 80 years with a median of 38 years. Fifteen patients were men (44%) and nineteen were women (56%). In these patients, detected causes of erythroblastopenia were MDS, idiopathic pure red cell aplasia (PRCA), parvovirus infection, post chemotherapy aplasia, plasma proliferative diseases, copper deficiency due to secondary amyloidosis, fever of unknown origin, hemophagocytic syndrome, enteric fever and legionella pneumonia. We found that between those reasons the most common causes of erythroblastopenia are MDS (17.7%) and idiopathic PRCA (17.7%). Discussion: As a result, erythroblastopenia in the bone marrow may be an early sign of MDS. In those AE cases possibility of being MDS must be kept in mind as it can be mistaken for PRCA. Conclusion: To conclude, in adults MDS without excess blast is one of the most common causes of erythroblastopenia in clinical practice and in case of erythroblastopenia the presence of MDS should be investigated.

Keywords: Erythroblastopenia, myelodisplastic syndrome, pure red cell aplasia

Introduction

Acquired erythroblastopenia (AE) is a rare clinical situation. It is characterized by the reduction of erythroid precursors in the bone marrow together with the low reticulocyte counts in the peripheral blood [1]. In AE the maturation of other bone marrow cell series are not affected. Various clinical findings could be related with AE, however, probably the best defined clinical picture associated with AE is pure red cell aplasia (PRCA) [2]. PRCA is classified in two main groups which are idiopathic and secondary. Age is an important issue for PRCA because adult PRCA cases are generally idiopathic.

Background

The main secondary causes of PRCA are drugs, Parvovirus B19 and other infectious reasons, lymphoid and myeloid neoplasia, autoimmune diseases, thymoma and pregnancy [2]. The best defined lymphoid and myeloid neoplasia associated with PRCA are large granular lymphocytic leukemia/lymphoma and myelodisplastic syndrome (MDS). In the literature the associations of those entities with PRCA are identified as only with case reports. There is no descriptive clinical trial regarding the etiology, frequency and clinical associations of PRCA and more moderate erythroblastopenia cases.

Aim

Herein, we aimed to assess the frequencies and clinical associations of AE by analyzing 12340 bone marrow samples in a retrospective manner.

Material and methods

Bone marrow aspirations which were obtained from patients who applied to Hacettepe

Table 1. The indications for performing bone marrow aspiration and biopsy in the studied patients

Indications	Number of patients		The patients being detected erythroblastopenia	
	Number	Rate (%)	Number	Rate (%)
Anemia of unknown origin	1427	27.2	7	0.49
Bicytopenia-pancytopenia of unknown origin	998	19	8	0.62
Unclassified MPD	726	13.8		
Isolated thrombocytopenia	473	9		
Staging-evaluation of lymphoproliferative diseases	403	7.7		
Fever of unknown origin	149	2.9	4	2.7
Organomegaly without any known cause	149	2.9		
Isolated leukopenia	132	2.5		
Hematologic neoplasia (follow-up)	788	15	15	1.9
Total	5245	100	34	0.64

Table 2. Age, hemoglobin level and reticulocyte count of acquired erythroblastopenia cases

	Female	Male	Total
	n=19 (56%)	n=15 (44%)	n=34
Age*	38 (16-69)	39 (17-80)	38 (16-80)
Hemoglobin**	10.38 ± 1.27	9.19 ± 2.04	9.86 ±1.73
Reticulocyte count**	1.43 ± 0.77	1.46 ± 0.90	1.45 ± 0.80

*Data were given as median (minimum-maximum). **Data were given as mean ± standard deviation.

Table 3. The causes of acquired erythroblastopenia in the studied population

The causes of erythroblastopenia	Frequency (patients' number)	Rate (%)
MDS	6	17.7
Idiopathic PRCA	6	17.7
Parvovirus infection	1	2.9
Post chemotherapy aplasia	15	44.3
Fever of unknown origin	1	2.9
MGUS	1	2.9
Deficiency of copper due to secondary amyloidosis	1	2.9
Hemophagocytic syndrome	1	2.9
S.typhi infection	1	2.9
Legionella pneumonia	1	2.9
Total	34	100

University Hematology Clinic between 2002 and 2013, were analyzed retrospectively. Informed consents were obtained from all patients as well as all of the ethical considerations had been strictly followed in accordance with the Helsinki declaration. The inclusion criteria of the cases were as, cases which have less than or equal to 5% proerythroblast plus erythroblast in count while they have less than 5% blastic cells, cases less than 10% plasma cells and less than 30% lymphocytes in count with normal cellularity. The exclusion criteria of cases were as, cases who had myeloproliferative disease (MPD), MDS/MPD and rebound myeloid hyperplasia after bone marrow aplasia or reduction of erythroid/myeloid rate due to G-CSF usage. In order to rule out erythroid suppression depending on blastic infiltration, the cases whose bone marrow biopsy results show blastic infiltration or which have more than 5% blasts and show no erythroblastopenia were also excluded. The clinical features of remaining cases evaluated from the data obtained from patients' files and computer records. Bone marrow aspiration reports had been recorded to a SQL type database which was prepared for this purpose prospectively

Statistical analyses

The data collected from SQL type database as in the Microsoft Excel 2007 and Statistical Packages for the Social Sciences v17.0 (SPSS Inc., Chicago, IL) software format and then descriptive statistical analysis was performed. Collected data were given as median (minimum-maximum) or mean ± standard deviation.

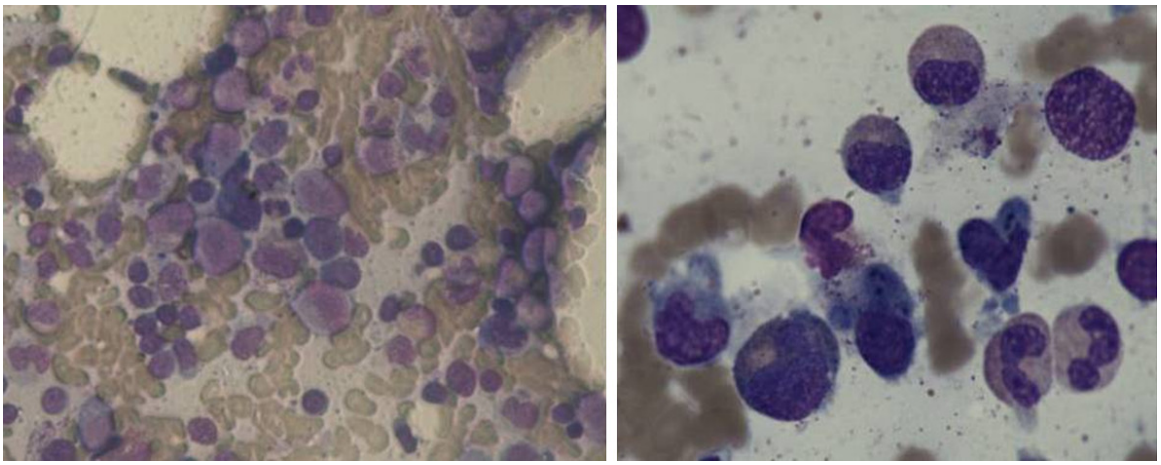

Figure 1. Erythroblastopenia in the bone marrow aspiration (depicting lower than 5% erythroblasts in bone marrow) during the clinicopathological follow-up of an adult patient with lymphoma.

Results

There were 12340 bone marrow analyzes which were reported from 6345 patients with hematological disorders. 9332 of those cases had bone marrow investigation reports that include successfully counted cells (5245 patients). The indications to perform bone marrow aspiration and biopsy in those patients were summarized in **Table 1**. Thirty four of evaluated 5245 patients (0.64%) have been accepted as erythroblastopenia according to the criteria above. Patient's age ranged from 16 to 80 years with a median of 38 years. Fifteen patients were men (44%) and nineteen were women (56%). Gender, age, hemoglobin levels and reticulocyte counts of these 34 patients were summarized in **Table 2**. The rates of detected erythroblastopenia during the investigation of etiology of anemia and bicytopenia-pancytopenia were 0.49% and 0.62%, respectively. Coincidentally detected erythroblastopenia rate by bone marrow aspiration investigation during the investigation of fever etiology and hematologic malignancy follow-up were 2.7% and 1.9%, respectively (**Table 1**). The final detected causes of erythroblastopenia were MDS, idiopathic PRCA, parvovirus infection, post chemotherapy aplasia, monoclonal gammopathy of undetermined significance (MGUS), copper deficiency due to secondary amyloidosis, fever of unknown etiology, hemophagocytic syndrome, S. typhi infection and legionella pneumonia (**Table 3**).

Discussion

There is no consensus for the rate of erythroblasts in bone marrow aspirate to define erythroblastopenia. In this study, the term "erythroblastopenia" has included the cases which have lower than or equal to 5% erythroblasts in bone marrow aspirate (**Figure 1**). This threshold value was determined according to the limited number of studies in the literature [3]. We have analyzed 34 erythroblastopenic patients' data retrospectively from our hospital records. In about 12 years of period, 34 erythroblastopenia cases had been seen in 12340 bone marrow aspiration reports as a frequency of 0.64%. Clinical studies about acquired erythroblastopenia are mostly case reports with review of the literature. In these studies, reported etiological causes of AE are infections such as parvovirus B19, human herpes virus, rarely Epstein Barr virus, drugs (phenytoin, isoniazid, azathioprine), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome), autoantibodies to erythroid precursors, thymoma, B cell lymphoproliferative disorders like as chronic lymphocytic leukemia or lymphoma and MDS [3-12]. However the exact percentages of etiologies did not presented in previous studies. The association of Parvovirus B19 and temporary erythroblastopenia of childhood and immune suppression associated erythroblastopenia were especially emphasized in the literature [13]. In regarding to the indications of performing bone marrow aspiration in our study, the highest erythroblastope-

nia detection rate was seen in the patients under investigation of fever etiology (2.7%). This result is not surprising because infectious agents can cause erythroblastopenia. The relationship between Parvovirus B19 and AE is well known [13]. However in this study parvovirus B19 is rarely detected as a cause of AE. This may be due to the absence of pediatric patients in our cohort who do not expose to viral infections previously and taking of appropriate precautions in immune compromised patients which are the other risk group. In our study, miscellaneous infectious disease, idiopathic PRCA and MDS were found to be closely related with AE. Similarly in other studies infectious diseases and idiopathic PRCA were found to be related AE. However we found MDS could be more frequently related to AE, which is a different finding from other studies [14]. With the exclusion of post chemotherapy aplasia cases, we found that the most common causes of erythroblastopenia are MDS and idiopathic PRCA (17.7%). The number of erythroblastopenic MDS cases were 6 (2.9% of 210) which have diagnosed during 2002-2013. Thus, erythroblastopenia in the bone marrow may be the early sign of MDS. In those AE cases possibility of being MDS must be kept in mind as it can be mistaken for PRCA [2]. In order to make the diagnosis of MDS earlier these findings can provide us to reach a better management of the disease. In our study, we have detected more ER in patients with MDS or PRCA and we propose that these results indicate high occurrence of ER in these patients. We ruled out the possibility of having more MDS or PRCA patients at the very beginning to screening for by our high number of bone marrow samples reported during more than a decade since data is collected by SQL type database bone marrow reporting program which is a routine-based hospital reporting program. However a future study may be designed which considers that issue. The histopathological examination of the bone marrow is a golden standard for the determination of erythroblastopenia. We have detected ER patients only with the method of bone marrow biopsy and no more patients were detected by any other means. However in future with the advancement of the next-generation bioinformatics methods new trials with larger number of patients may be conducted.

This is the first study in the literature that investigated a large series of bone marrow samples to detect erythroblastopenia in adults. Also first time in the literature, the percentages of erythroblastopenia is well defined in the patients who were performed bone marrow aspiration by any reason (0.64%). Moreover, in our study the percentages of the erythroblastopenia causes are stated clearly, different from other studies. To conclude, in adults MDS without excess blast is one of the most common causes of erythroblastopenia in clinic practice if cases that were given myelotoxic chemotherapy are excluded and in case of erythroblastopenia the presence of MDS should be investigated. These are unique epidemiologic findings and should be confirmed with future studies that preferably conducted prospectively.

Disclosure of conflict of interest

None.

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