EFFECT OF PLASMA CELLS PERCENTAGE AND PATTERN OF INFILTRATION ON HEMATOLOGICAL PARAMETERS

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ABSTRACT

Introduction: Anemia has been documented in more than two thirds patients of myeloma. There are multiple reasons for this, some of which comprise anemia of chronic disorders, reduced erythropoietin production, decreased sensitivity of erythroid precursors and myeloma cell mediated apoptosis of erythroid progenitors. Crowding of marrow by plasma cells and replacement of marrow interferes with hematopoiesis and is also accountable for anemia.

Objective: To see the effect of percentage and pattern of infiltration of plasma cells on various hematological parameters.

Material and Methods: Prospective study, conducted in Department of Pathology, Pakistan Institute of Medical Sciences Islamabad, for a period of 2 years. Total 78 patients were included in the study. Patients having increased plasma cells on bone marrow aspirate were included in this study. Patients with history of chemotherapy, nutritional deficiency or any other comorbid were excluded in this study. Patients were categorized according to number of plasma cells on bone marrow aspirate as: 5 – 20%, 21 – 30%, 31 – 40%, 41 – 50%, 51-60%, 61 – 70%, 71 – 80%, >80%. Patients were also categorized according to pattern of infiltration on bone marrow trephine biopsy as: Focal, interstitial and diffuse patterns.

Results: A total of 78 patients were selected for the study. Male to female ratio was (2:1). Hematological parameters i.e. hemoglobin, red blood cells, white blood cells and platelets etc. were shown to be deranged as number of plasma cells were increasing and pattern of infiltration was focal to diffuse. There was statistically significant difference between hemoglobin, red blood cells and nucleated red blood cells in patients having <10% and >10% plasma cells on bone marrow aspiration.

Key Words: Plasma cells, plasma cell dyscrasia, Hematological parameters, Bone marrow biopsy, Infiltration.

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INTRODUCTION

Plasma cells are terminally differentiated from B – cell lineage which are responsible for production of large amount of immunoglobulins [1,2]. Plasma cell dyscrasia is group of broad spectrum diseases which are characterized by accumulation and proliferation of cells which produce monoclonal antibodies [3]. It includes monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, smoldering multiple myeloma, plasma cell leukemia, Waldenstrom's macroglobulinemia (WM) POEMS syndrome, heavy chain disease plasmacytoma and amyloidosis [4-6].

Plasma cells have impact on functions of normal haemopoietic cells. They may impair the structure and function of erythroblastic islands by secreting various cytokines [7-9]. Myeloma cells secrete transforming growth factor – β (TGF – β) which impair adhesion and growth of early progenitor cells, ultimately reducing Colony Forming Unit – Erythroid (CFU – E). Myeloma cells also express FAS ligand and tumor necrotic factor – related apoptosis – inducing ligand [10-12]. Patients suffering from myeloma usually have decreased production of erythropoietin (EPO) due to renal impairment caused by accumulation of monoclonal immunoglobulin or light chain component [13]. Myeloma cells also produce bone morphogenic protein – 2 (BMP2) which induce hepcidin, ultimately restricts iron required by late stage erythroblasts for production of hemoglobin [14-16]. Plasma cells affect the microenvironment of bone marrow by their pattern of infiltration and quantity in bone marrow.

We conducted a study at our center to determine the effect of percentage of plasma cells and pattern of infiltration in bone marrow on various hematological parameters.

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MATERIAL AND METHODS

It was a prospective study, conducted in Department of Pathology, Pakistan Institute of Medical Sciences Islamabad, for a period of 2 years. Total 78 patients were included in the study. Patients having increased plasma cells on bone marrow aspirate were included in this study. Patients with history of chemotherapy, nutritional deficiency or any other co-morbid were excluded in this study. Nutritional deficiency was excluded by performing complete blood count, iron and folate studies. Blood CP was performed using Automated Hematology Analyzer Sysmex XP-100. Hematological parameters were hemoglobin level, red blood cell count, white blood cell count, platelet count and nucleated red blood cells. Bone marrow aspiration was performed after explaining procedure to patients and appropriate consent. Samples were taken from posterior superior iliac spine after giving local anesthesia. Bone marrow aspirate slides were stained using Wright's stain while Trephine sample was stained using H & E stain. 500 cells were counted on bone marrow aspirate samples and number of all cells including granulocytes, erythrocytes, lymphocytes and plasma cells were counted accordingly, Patients were categorized according to number of plasma cells on bone marrow aspirate as: 5 – 10%, 11 – 20%, 21 – 30%, 31 – 40%, 41-50%, 51 – 60%, 61 – 70%, >80%. Patients were also categorized according to pattern of infiltration on bone marrow trephine biopsy as: Focal (nodular), interstitial and diffuse patterns. All date were analyzed using SPSS 21.0. P – value of <0.05 was considered statically significant.

RESULTS

A total of newly diagnosed cases of multiple myeloma were included in study were 78 patients. Out of 78 patients 52 were male and 26 were female (Figure-1). Male to female ratio was (2:1). Age of patients was ranged between 45 to 80 years with a mean age of 61.5 ±3.4 years. Patients were categorized into 2 classes. Class 1 was based on number of plasma cells on bone marrow aspirate. Out of 78 patients, 19 patients (24.35%) had 2 – 10% plasma cells, 13 patients (16.66%) had 11 – 20% plasma cells, 5 patients (6.41%) had 21 – 30% plasma cells, 11 patients (14.10%) had 31 – 40% plasma cells, 9 patients (11.53%) had 41 – 50% plasma cells, 10 patients (12.82%) had 51 –60% plasma cells, 5 patients (6.41%) had 61 – 70% plasma cells and 7 patients (8.97%) had more than 70% plasma cells in bone marrow aspirate (Figure-2). Difference of hematological parameters was assessed in all groups (Table-1). Pattern of infiltration of plasma cells on bone marrow trephine biopsy, as focal, interstitial and diffuse pattern is shown in Table-2. Out of 78 patients, 31 patients (39.74%) had focal infiltration, 26 patients (33.33%) had interstitial infiltration and 21 patients (26.92%) had diffuse infiltration (Figure-2). Hematological parameters were assessed in all groups (Table-2), and patients were then categorized into two groups based on cut – of – value of 10% plasma cells (Table-3). T – test was applied to see significance. Bone marrow showed hypercellularity with presence of plasma cells in different numbers throughout the study. Plasma cells were oval with round eccentric nucleus without nucleoli, having abundant cytoplasm and perinuclear hof.

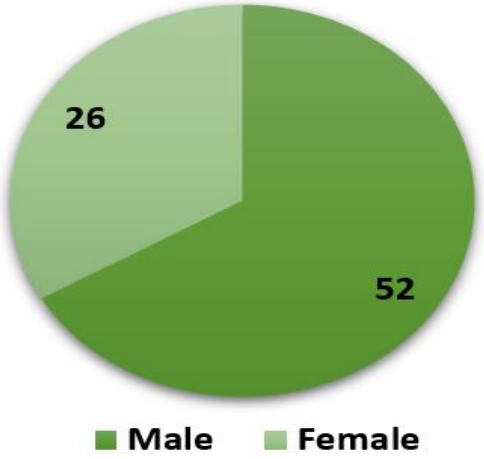

Figure-1: Number of patients according to gender.

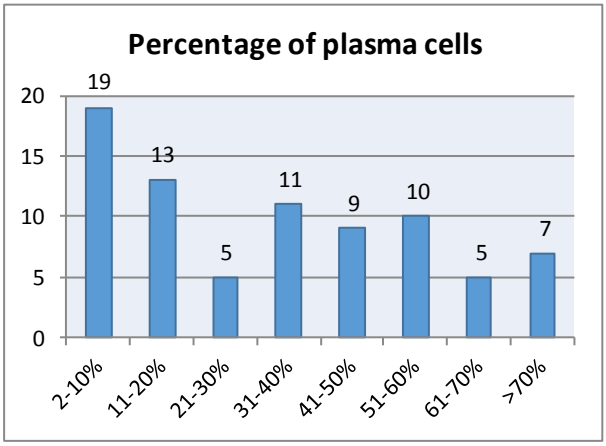

Figure-2: Number of patients according to percentage of plasma cells.

Table-1: Difference in hematological parameters according to percentage of plasma cells.

Parameter	5-10% (n=19)	11-20% (n=13)	21-30% (n=5)	31-40% (n=11)	41-50% (n=9)	51-60% (n=10)	61-70% (n=5)	>70% (n=7)
Mean Hemoglobin (g/dL)	11.31± 1.21	9.31 ± 1.10	9.13 ± 1.48	8.94 ± 1.87	9.02 ± 1.09	8.71 ± 1.23	7.74 ± 1.32	6.99 ± 1.44
Mean RBC Count (millions/mm^3)	4.31±0.31	3.13 ± 0.87	3.47 ± 0.41	3.18 ± 0.47	3.81 ± 0.31	2.87 ± 0.91	3.01 ± 1.03	2.80 ± 0.84
Mean WBC count (X10^9/L)	7.23±2.41	4.52 ± 1.34	5.23 ± 1.21	4.24 ± 1.42	4.38 ± 1.48	4.87 ± 1.98	4.03 ±1.89	3.87 ±0.98
Mean Platelets (10^9/L)	472± 112.12	423 ±182.21	357 ±162.32	404 ±187.52	396±143.33	373	415	383
Mean Nucleated RBC	4.21 ±0.02	1.91± 0.08	-	-	2.01 ± 0.04	-	-	1.08 ± 0.01

Table-2: Difference in hematological parameters according to pattern of infiltration.

Parameter	Focal (n=31)	Interstitial (n=26)	Diffuse (n=21)
Mean Hemoglobin (g/dL)	11.41±2.12	9.31±1.93	7.43±1.42
Mean RBC Count (millions/mm^3)	4.12±1.20	3.68±1.03	2.91±1.41
Mean WBC count (X10^9/L)	8.42±1.97	5.32±.32	3.49±1.18
Mean Platelets (10^9/L)	412	241	201
Mean Nucleated RBC	3.12±1.01	1.02±0.21	1.77±1.87

Table-1: Difference in hematological parameters according to number of plasma cells

Parameter	Plasma cells (<10%)	Plasma cells (>10%)	P – value
Mean Hemoglobin (g/dL)	11.4±1.31	9.76±1.53	0.013
Mean RBC Count (millions/mm^3)	4.32±0.65	3.52 ± 0.76	0.042
Mean WBC count (X10^9/L)	7.54±1.64	6.74±1.57	0.64
Mean Platelets (10^9/L)	427±68.43	396±97.54	1.21
Mean Nucleated RBC	2.31±0.23	-	<0.001

DISCUSSION

Increase in number of plasma cells has various effects on hemopoiesis as well as other basic hematological functions [10-17]. Beside the secretion of various cytokines by plasma cells, there is also decrease in number and functioning of normal hemopoietic cells as there is infiltration and replacement by myeloma cells [14,18,19]. In this study, it was shown that hemoglobin, red blood cell count (RBC) and white blood cell count (WBC) were decreasing as number of plasma cells increased, suggesting the down-regulation of normal erythropoiesis and granulopoeisis by myeloma cells. Platelet count did not show any significant change. Although nucleated red blood cells (nRBCs) were variable in different groups, suggesting the effect of ineffective erythropoiesis. On trephine biopsy examination, most of the patients were having focal infiltration of plasma cells, as many patients were diagnosed at early stage of disease. It was shown that hemoglobin, red blood cell (RBC) and white blood cell (WBC) counts were progressively declining from focal to diffuse infiltration. This strongly suggests the replacement of normal hemopoeitic tissue by myeloma cells. Platelet count was also progressively declining from focal to interstitial. Nucleated red blood cells (nRBCs) were variable across all groups. This suggests that bone marrow trephine examination was more reliable for functioning of thrombopoiesis as compared to bone marrow aspiration. While dividing patients into cut – of – values of 10% plasma cells, it was found that hemoglobin, red blood cell count and nucleated red blood cells were significantly different in both groups ($p<0.05$). Although platelet and white blood cells did not show any significant difference ($p>0.05$). There are only few studies showing effect of plasma cells on hemopoietic cells. Study performed by Stifter *et al* showed that combined evaluation of both bone marrow aspiration and trephine biopsy was more accurate as compared to single along [20]. Our study favors in this point that trephine biopsy examination showed additional information about platelet count. Anass *et al* proved in his study that myeloma cells are responsible for causing anemia by deranging the erythropoiesis [14]. This is first study to classify the number and pattern of infiltration of plasma cells and compare their effect on various hematological parameters including hemoglobin, red blood cells, white blood cells and platelets.

CONCLUSION

Number and pattern of infiltration significantly affects production of hemoglobin, red blood cell count and white blood cell count. So appropriate conservative management along with conventional treatment can be done accordingly. It also helps in assumption of pattern of infiltration when clinical presentation and noninvasive investigations are strongly supportive of plasmacytosis. Along with other interventional and non – interventional methods for evaluation of prognosis, percentage of plasma cells and pattern of infiltration should also be taken as an additional tool. More studies on large population should be done to evaluate and make strong evidence of effect of plasma/myeloma cells on hemopoietic cells.

AUTHORS CONTRIBUTION

Shahzad Ali Jiskani: Data Collection, Literature Review, Statistical Analysis, Discussion
Sundas Ali: Data Collection, Discussion
Aliena Sohail: Data Collection, Literature Review
Lubna Naseem: Literature Review
Asfa Zawar: Data Collection
Humaira Rizwan: Literature Review, Discussion
Sarah Jamal: Data Collection
Asma Mustafa, Bushra Anam Ali, Maryam Zulfiqar: Data Collection, Discussion

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