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Correlation between Peripheral Blood Thrombocytopenia and Bone Marrow Findings – A Study of 100 Cases.

Ashima Jain[1], Mohanvir Kaur[2], Arun Puri[3], Navjot Kaur[4], Javia Singh Raina[4]

[1]Senior Resident, Department of Pathology, Government Medical College, Patiala.
[2]Assistant Professor, Department of Pathology, Government Medical College, Patiala.
[3]Professor, Department of Pathology, Government Medical College, Patiala.
[4]Junior Resident, Department of Pathology, Government Medical College, Patiala.

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ABSTRACT

Background: Thrombocytopenia (platelet count less than 150,000/µl) is commonly encountered in routine hematological investigations. Here we present a study done to understand the prevalence of various conditions leading to thrombocytopenia, referred for bone marrow examination. It is a retrospective study done on 100 cases of thrombocytopenia referred for bone marrow examination in a tertiary care hospital from January 2016 to October 2016. The commonest cause of thrombocytopenia for which bone marrow was sought came out to be megaloblastic anemia followed by acute leukemia and aplastic anemia. Aim: Calculate the prevalence of various conditions causing thrombocytopenia, in cases referred for bone marrow examination, and Understand the various megakaryocytic alterations in hematological disorders presenting with thrombocytopenia due to different mechanisms. **Methods:** A retrospective study was done on 100 patients of thrombocytopenia referred for bone-marrow aspiration in a tertiary care hospital catering to both rural and urban population from January 2016 to October 2016. All cases of thrombocytopenia (platelet count less than 1,50,000/µl) diagnosed on hematology analyzer and later confirmed by peripheral blood film examination, referred for bone marrow examination for various reasons were included in this study. Stained bone-marrow aspirate smears were examined. Records regarding the clinical indication for the procedure, peripheral blood smear reports, blood counts and significant findings on bone-marrow aspiration smears were retrieved. The role of bone-marrow aspiration in the diagnosis of hematological and non- hematological disorders was reviewed in the study. **Results:** The commonest cause of thrombocytopenia for which bone marrow examination was sought was megaloblastic anemia(76%), followed by acute leukemia(7%), aplastic anemia(5%), myelodysplastic syndrome (4%) which was followed by ITP(3%), and one case each of gelatinous marrow transformation, malaria and NHL spillover. **Conclusion:** Further studies on the evaluation of megakaryocytic alteration and their contribution to thrombocytopenia can provide growing knowledge to the pathogenesis of numerous hematopoietic disorders that may identify broader clinical applications of the newer strategies to regulate platelet count and functioning.

Keywords: Megakaryocytes, Thrombocytopenia, Bone marrow.

INTRODUCTION

Platelets are formed and released into the bloodstream by precursor cells called megakaryocytes (MK) that are derived from haematopoietic stem cells (HSCs), which evolve from the multipotential haemangioblast. Mature MKs give rise to circulating platelets by the acquisition of the cytoplasmic structural and functional characteristics necessary for platelet action,[1,2] reaching cell sizes <50-100 microns in diameter and ploidy ranging up to 128 N.[3,4] Endoreduplication (polyploidisation) and expansion of cytoplasmic mass are the hallmarks of MK maturation.[5] The production of platelets by megakaryocytes requires an intricate series of remodeling events that result in the release of thousands of platelets from a single megakaryocyte. Abnormalities in this process can result in clinically significant disorders. A diversity of factors can contribute to anomalous platelet counts; one of these is inappropriate platelet production. Thrombocytopenia (platelet counts less than 150,000/µl) can lead to inadequate clot formation and increased risk of bleeding.[6] The present study was undertaken to calculate the prevalence of various conditions associated with thrombocytopenia and to record the megakaryocytic alterations in various cases of thrombocytopenia.

Name & Address of Corresponding Author
Dr Mohanvir Kaur,
Assistant Professor,
Department of Pathology,
Government Medical College, Patiala.

MATERIALS AND METHODS

A retrospective series of 100 bone marrow aspirations was conducted in a tertiary care centre

catering to both urban as well as rural population in north India. All the cases of thrombocytopenia which were diagnosed on hematology analyzer (platelet count < 1, 50,000); confirmed subsequently by peripheral smears and referred for bone marrow examination for various reasons from January 2016 to October 2016 were taken up for the study. Slides of BMA (leishman stained) were retrieved and studied. The clinical details, complete blood counts, and other relevant laboratory investigations were also obtained.

In the present study for scoring purposes the number and morphological changes were pre-defined before start of the study. The number of the megakaryocytes was considered as normal (one megakaryocyte per one to three low-power fields), increased (more than two megakaryocytes per low-power field) or decreased (one megakaryocyte per five to ten low-power fields).[7]

The presence of abnormal megakaryocytes which included the micromegakaryocytes, dysplastic forms, megakaryocytes with separated lobes and hypogranular forms were considered as dysmegakaryocytopoiesis [Table 1 & Figure 1].[22]

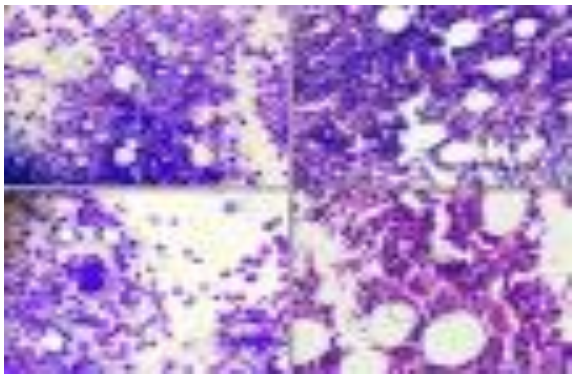

Figure 1: A: Collection of hypolobated megakaryocytes in bone marrow aspirate. (MGG 400 X) B: Collection of hypolobated megakaryocytes in bone marrow biopsy section. (H& E 100X) C: Highpower view of a hypolobated immature megakaryocyte in aspirate. (MGG

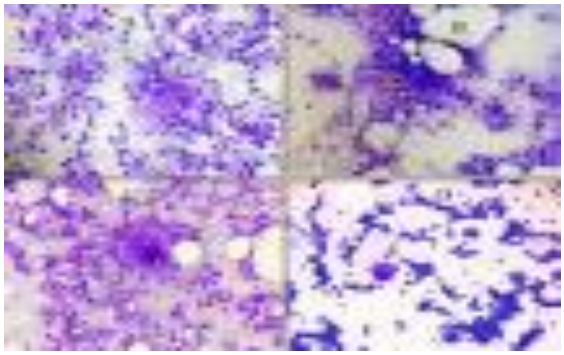

Figure 2: A: Multi nucleated dysplastic form of megakaryocyte in bone marrow aspirate. (MGG 400 X) B: Cytoplasmic vacuolization of megakaryocytes noted in infection associated thrombocytopenia (IAT). (MGG 100 X) C: Emperiopolesis in megakaryocytes. (MGG 1000 X)

RESULTS

1. 57% patients in the present study presented with low grade fever.
2. Conditions leading to thrombocytopenia in present study

Sr. no.	condition	percentage
1.	Megaloblastic anemia	76%
2.	Acute leukemia	7%
3.	Aplastic anemia	5%
4.	MDS	4%
5.	ITP	3%
6.	CML	2%
7.	Gelatinous transformation	1%
8.	Malaria infection	1%
9.	NHL	1%

Most common cause of thrombocytopenia came out to be megaloblastic anemia.

3. Observations in cases of megaloblastic anemia cases
   a. Age and sex distribution of megaloblastic anemia

Age groups	M	F	Total
0-10	4	7	11
11-20	11	15	26
21-30	8	7	15
31-50	10	10	20
Above 50	13	15	28

As seen, megaloblastic anemia is relatively more common in females in our set up.

   b. Number of megakaryocytes in cases of megaloblastic anemia

Sr.no.	Number	Cases (total 76)	percentage
1.	Normal	21	27.6%
2.	Increased	21	27.6%
3.	Decreased	34	44.7%

Megakaryocytes were reduced in majority cases.

   c. Megakaryocyte morphology alterations in cases of megaloblastic anemia

Sr.no.	morphology	Number of megakaryocytes (76 cases)	percentage
1.	normal	30	39.4%
2.	hyperlobated	16	21%
3.	Immature forms	12	15.8%
4.	hypernucleated	9	11.8%
5.	hypolated	5	6.6%

4. Micromegakaryocytes were seen in cases of CML.
5. Immature forms and shift to left was seen in the cases of ITP.
6. Age, sex distribution, presentation and morphology of megakaryocytes in cases of MDS:
   a. All the 4 patients of MDS were above 50 years of age.
   b. All of them presented with fever.

c. All patients had decreased megakaryocytes in bone marrow.
d. 3of the 4 patients had hypolobated megakaryocytes and one patient had hypernucleated megakaryocytes.

7. Megakaryocytes were markedly reduced or absent in cases of acute leukemia, aplastic anemia and gelatinous marrow transformation.

DISCUSSION & CONCLUSION

MK and platelets, which are their progeny, are highly specialized cells that participate in hemostatic and inflammatory functions. Since each platelet lives only about 10 days, the platelet supply is continually renewed by production of new platelets from the maturation of MK.[8]

Conventionally a normal megakaryocyte has four to sixteen nuclear lobes and an immature megakaryocyte is defined as a young form of megakaryocyte having scant bluish cytoplasm and lacking lobulation of the nucleus which occupies almost all of the cell. Dysplastic megakaryocytes were defined as those with single/ multiple separate nuclei.

Micromegakaryocytes were defined as megakaryocytes whose size was that of a large lymphocyte/ monocyte and which had a single/bilobed nucleus. The megakaryocytes were considered to show platelet budding if there was budding of cytoplasmic processes from their surfaces. Micromegakaryocytes were seen in cases of CML.

A shift to young, immature, less polypoid megakaryocytes and fewer mature platelet-producing megakaryocytes was the outstanding morphological feature noted in almost all the cases of ITP in the present study. Similar findings were observed by Houwerzijl et al.,[7] Deka L et al., observed that megakaryocytes in cases of ITP showed a higher nuclear/cytoplasmic ratio, lower nuclear roundness factor and lower nuclear contour ratio. Cellular circularity and compactness were significantly different in ITP as compared to non-ITP cases, indicating that the megakaryocytes were less round in ITP subjects.[10]

Megaloblastic anemia presents with different manifestations as observed in present study. Pallor and weakness seen in all patient this is due to ineffective haematopoiesis lead to decreased life span of RBC and to premature destruction of developing megaloblasts in the marrow resulting low hemoglobin level. In present study, low grade fever was seen in 47 of 76 (61.8%) cases where as a study carried out by Sunil et al. mention 65.5% of patients presented with low grade fever. Fever was significantly the commonest cause for infection to which the individual is much more susceptible due to impaired intracellular killing of ingested bacteria by neutrophils and macrophages.

Bicytopenia was reported in 40.7% cases and pancytopenia in 59.2% cases in present study. Megaloblastic anemia is an important cause of cytopenia (pancytopenia and bicytopenia). Study carried out by Sarode et al reported an incidence of pancytopenia in 43.8% and bicytopenia in 80.5% cases.

MDS is common in older age group. 4 cases were recorded in the present study. All of them were more than 50 years of age. All the patients presented with fever. All had reduced number of megakaryocytes on bone marrow examination. 3 of the 4 patients had hypolobated megakaryocytes and one patient showed hypernucleated megakaryocytes.

Since, bone marrow findings in cases of thrombocytopenia give a definite diagnosis of the underlying pathomechanism, bone marrow study is frequently asked in cases of thrombocytopenia. The findings of decrease in megakaryocytes in aplastic anemia, gelatinous marrow transformation and leukemia, and increase in the number of megakaryocytes in immune thrombocytopenia were consistent with other studies.

Further studies on the evaluation of megakaryocytic alteration and their contribution to thrombocytopenia can provide growing knowledge to the pathogenesis of numerous hematopoietic disorders that may identify broader clinical applications of the newer strategies to regulate platelet count and functioning.

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