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A STUDY OF MEGAKARYOCYTIC CHANGES IN THROMBOCYTOPENIA IN BONE MARROW ASPIRATION AND BIOPSY AT TERTIARY CARE CENTER.

Pathology

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ABSTRACT

Introduction: Thrombocytopenia is common clinical entity with varied differential diagnosis and presents in various clinical diseases. Mostly thrombocytopenia, either persistent, isolated or in association with pancytopenia refractory to treatment is one of the commonly encountered hematological problems for which a bone marrow study is indicated.

Aims and objective: To evaluate the megakaryocytic changes in the bone marrow aspiration and bone marrow biopsy in cases of thrombocytopenia and their relationship with underlying etiology and to find out the proportion of various conditions associated with thrombocytopenia and associated megakaryocytic changes.

Material and methods: This study was carried out at department of pathology at a tertiary care center from period between June 2017 todecember 2019

Observation and results: Most common etiology of thrombocytopenia was myelodysplastic syndrome (33%) out of total of 64 cases.

The most common cause of thrombocytopenia was MDS (33%) followed by MA (20%) and ITP (16%).25 cases (40%) show dysplastic changes of megakaryocytes ,most of them seen in (17 cases out of 21) myelodysplastic syndrome (MDS) .

Hypolobated form were seen in 65% cases of thrombocytopenia which were mostly seen in MDS (77.7%).Immature form seen in 17% (11 cases), dwarf form were seen in 20% (13 cases), bare form were seen in 6% (4 cases). 4.5 % (3 cases) show budding.Emperipolesis was seen only case of thrombocytopenia caused by MDS. The finding of Cytoplasmic vacuolization was seen in one case of ITP.

Conclusion: This study may be help in early diagnosis in various hematopoietic disorder.Mere presence of dysplastic changes only should not be straight forward for diagnosis of myelodysplastic syndrome, other hematological parameters and complete clinical history is required to correlate.

KEYWORDS

Megakaryocyte, Thrombocytopenia, Dysplastic Changes

INTRODUCTION

Platelets are anucleated cell fragments released into the blood stream by precursor cells called megakaryocytes (MKs) that are derived from haematopoietic stem cells (HSCs), which evolve from the multipotentialhaemangioblast.Mature MKs give rise to circulating platelets by the acquisition of the cytoplasmic structural and functional characteristics necessary for platelet action.The stages of maturation are megakaryoblast, promegakaryocytes, granular megakaryocytes, mature megakaryocytes and release of platelets. Defect in any of these stages of megakaryocytopoiesis may result in thrombocytopenia. Megakaryopoiesis is regulated both by cell autonomous process, such as transcriptional regulation and by extracellular cues dominated by thrombopoietin (TPO) that binds to its receptor.Patients presenting with thrombocytopenia most likely have an acute infection, heparin-induced thrombocytopenia, liver disease, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, or a hematologic disorder. During pregnancy, preeclampsia and the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome are associated with thrombocytopenia. Patients with isolated thrombocytopenia commonly have drug-induced thrombocytopenia, immune thrombocytopenic purpura, pseudo-thrombocytopenia, or if pregnant, gestational thrombocytopenia.Various studies have highlighted the dysplastic morphology of megakaryocytes in thrombocytopenia associated with myelodysplastic syndromes (MDS) and non MDS conditions.

Dysplastic features of megakaryocyte morphology include multiple separated nuclei, micromegakaryocytes (3-6 times larger than RBC with 1-2 lobes, mature nucleus and lower nuclear to cytoplasmic ratio) and hypogranular forms (with little or no granules). Non dysplastic features of megakaryocytes include immature forms (with basophilic cytoplasm, high nuclear to cytoplasmic ratio and no nuclear lobation), emperipolesis (intact hematopoietic cells within cytoplasm) cytoplasmic budding, vacuolization and bare nuclei without cytoplasm.[6]This study was undertaken to identify the alterations in number and morphology of megakaryocytes in different hematopathological disorders causing thrombocytopenia and to evaluate if these alterations have any significant association with different causes of thrombocytopenia.

Aims and objectives: To evaluate the megakaryocytic changes in the bone marrow aspiration and bone marrow biopsy in cases of thrombocytopenia and their relationship with underlying etiology and to find out the proportion of various conditions associated with thrombocytopenia and associated megakaryocytic changes.

Observation and Results

In present study, most common etiology of thrombocytopenia was myelodysplastic syndrome (33%) followed by Megaloblastic anemia (20%) and idiopathic thrombocytopenic purpura (16%).

Table 1 Etiology of thrombocytopenia in present study

Sr. No.	Disease	No. of cases	Percentage (%)
1.	Myelodysplastic syndrome	21	33
2.	Megaloblastic anemia	13	20
3.	Idiopathic thrombocytopenic purpura	10	16
4.	Dimorphic anemia	8	13
5.	Acute leukemia	6	9
6.	Acute myeloid leukemia	2	3
7.	Acute lymphocytic leukemia	1	1.5
8.	Chronic lymphocytic leukemia	1	1.5
9.	Chronic Lympho proliferative neoplasm	1	1.5
10.	Plasma cell dyscrasia	1	1.5
11.	Total	64	100

Table 2 Distributions according to no. megakaryocytes in present study. (Number per low power field)

Sr. No.	Etiology of thrombocytopenia	No. of cases	Normal	Increased	Decreased	Absent
1.	Myelodysplastic syndrome	21	18	1	2	0
2.	Megaloblastic anemia	13	10	1	2	0
3.	Idiopathic thrombocytopenic purpura	10	2	8	0	0

4.	Dimorphic anemia	8	5	0	2	1
5.	Acute leukemia	6	0	0	0	6
6.	Acute myeloid leukemia	2	2	0	0	0
7.	Acute lymphocytic leukemia	1	0	0	0	1
8.	Chronic lymphocytic leukemia	1	0	0	0	1
9.	Chronic Lympho-proliferative neoplasm	1	0	0	1	0
10.	Plasma cell dyscrasia	1	1	0	0	0
11.	Total	64				

Table 3 Various morphology changes in megakaryocytes in different causes of thrombocytopenia in present study.

Sr. No.	Disease	No. of cases	Hypolobated	Micromega.	Multiple separate nuclei	Hypergranular Form	Hypogranular Form	Dwarf Form	Bare Form	Budding	Emperipolesis	Cytoplasmic Vacuolation	Immature Form
1.	Myelodysplastic syndrome	21	18	12	17	1	1	6	2	2	1	0	1
2.	Megaloblastic anemia	13	9	1	4	0	0	5	1	0	0	0	2
3.	Idiopathic thrombocytopenic purpura	10	8	3	2	1	1	2	1	1	0	1	6
4.	Dimorphic anemia	8	3	0	0	1	1	0	0	0	0	0	0
5.	Acute leukemia	6	0	0	0	0	0	0	0	0	0	0	0
6.	Acute myeloid leukemia	2	1	0	0	0	0	0	0	0	0	0	1
7.	Acute lymphocytic leukemia	1	0	0	0	0	0	0	0	0	0	0	0
8.	Chronic lymphocytic leukemia	1	0	0	0	0	0	0	0	0	0	0	0
9.	Chronic Lympho-proliferative neoplasm	1	1	0	0	0	0	0	0	0	0	0	1
10.	Plasma cell dyscrasia	1	1	0	0	0	0	0	0	0	0	0	0
11.	Total	64	41	16	23	3	3	13	4	3	1	1	11

In present study, total of 64 cases of thrombocytopenia were included in which 46 cases (72%) were observed in male and 18 cases (28%) were females. Thrombocytopenia was most common in the age group of 11-20 years (20%; 13 cases) and least age group 51-60years (7%, 5 cases).

The most common cause of thrombocytopenia was MDS (33%) followed by MA (20%) and ITP (16%). Bone marrow cellularity was normal in 65% cases followed by hypercellularity which was seen in 27% and hypocellular in 8% .Increased numbers of megakaryocytes were seen in 10 cases (16%) out of 64 cases which was mostly seen in ITP. Decreased numbers of megakaryocytes were seen in 11 % . Megakaryocytes were absent in 14 % of cases of thrombocytopenia in present study. 25 cases (40%) show dysplastic changes of megakaryocytes ,most of them seen in (17 cases out of 21) myelodysplastic syndrome (MDS) are well known;Hypolobated form were seen in 65% cases of thrombocytopenia which were mostly seen in MDS (77.7%).Immature form seen in 17% (11 cases) of thrombocytopenia in present study. Dwarf form were seen in 20% (13 cases) in present study. Bare form were seen in 6% (4 cases). 4.5 % (3 cases) show budding.Emperipolesis was seen only case of thrombocytopenia caused by MDS. The finding of Cytoplasmic vacuolization was seen in one case of ITP.

DISCUSSION

Thrombocytopenia is common clinical entity with varied differential diagnosis and presents in various clinical diseases. Mostly thrombocytopenia, either persistent, isolated or in association with pancytopenia refractory to treatment is one of the commonly encountered hematological problems for which a bone marrow study is indicated.In present study, total of 64 cases of thrombocytopenia were included in which 46 cases (72%) were observed in male and 18 cases (28%) were female with male predominance similarly in the studies done by Vinayakamurthy et al[36] and Choudhary et al[7] with male predominance.

Thrombocytopenia was most common in the age group of 11-20 years (20%; 13 cases) and least age group 51-60years (7%, 5 cases). In contrast a study by Vinayakamurthyet al[10] found age group 30-39 years was most common. In a study by Muhuryet al[11], less than 10 year was most common age group. Less than 20 years age group were found in study by Pokharelet al.[9]

In both study by Muhury[11] et al and Vinayakamurthyet al[10], MDS cases in thrombocytopenia was excluded, their study included only non-MDS cases.

The most common cause of thrombocytopenia was MDS (33%) followed by MA (20%) and ITP (16%). In contrast the most common cause of thrombocytopenia was megaloblastic anemia found in other studies by Choudharyet al[7], Das et al[11] and Deepika et al.[5] In a study by Bhasin et al[4] found, dimorphic anemia most common cause of thrombocytopenia. ITP was most common cause found in a study done by Gupta et al.[8] Acute leukemia was second leading cause of thrombocytopenia in a study by Muhury et al.[11]

Sr. No.	Study	No. of cases	Most common cause	Second common cause
1.	Muhury et al[11]	144	Acute leukemia (31.3%)	ITP (13.15%)
2.	Choudary et al[30]	139	Megaloblastic anemia (31.7%)	ITP (27.3%)
3.	Das et al[38]	80	Megaloblastic anemia (47.5%)	Haematological malignancy (32.5%)
4.	Bhasin et al[4]	60	Dimorphic anemia (30%)	MDS (10%)
5.	Gupta et al[31]	50	ITP (34%)	Megaloblastic anemia (24%)
6.	Deepika et al[5]	100	Megaloblastic anemia (33%)	Acute leukemia (21%)
7.	Present study	64	MDS (33%)	Megaloblastic anemia (20%)

In the present study, Megaloblastic anemia was second common cause of thrombocytopenia similar in the study done by Gupta et al[31] and Tirumalasetti et al.[34] In the present study, bone marrow cellularity was normal in 65% cases followed by hypercellularity which was seen in 27% and hypocellular in 8% in contrast to 9% , 79% and 12%, respectively in a study by Deepika et al.[5]

In the present study, increased numbers of megakaryocytes were seen in 10 cases (16%) out of 64 cases which was mostly seen in ITP, comparable to a study by Muhuryet al[11] and Deepika et al[5], 31 % and 16 %. Decreased numbers of megakaryocytes were seen in 11 % in contrast to a study by Muhuryet al[11] and Deepika et al[5] which was 25 % and 31 %. Megakaryocytes were absent in 14 % of cases of thrombocytopenia in present study, in contrast other studies were 14% and 24% by Deepika et al[5] and Muhury et al[11] respectively.

25 cases (40%) show dysplastic changes of megakaryocytes ,most of them seen in (17 cases out of 21) myelodysplastic syndrome (MDS) are well known; however, full hematological knowledge can differentiate such changes from similar morphological changes of megakaryocytes in other diseases like, dimorphic anemia, idiopathic thrombocytopenic purpura, megaloblastic anemia and acute leukemia. Dysplastic form included micromegakaryocytes, multiple separate nuclei and hypogranular form.

Among non-dysplastic features, the most common were hypolobated form, Immature form, dwarf form, bare form, budding, emperipolesis and cytoplasmic vacuolation form.

Table 4 Dysplastic changes in various present study with comparable to other studies.

Sr. No.	Study	No. of cases	MDS	NON MDS
1.	Muhury et al[11]	144	77.7 %	50%
2.	Bhasin et al[4]	60	67%	21%
3.	Deepika et al[5]	100	100%	33%
4.	Present study	64	81%	19%

Hypolobated form were seen in 65% cases of thrombocytopenia which were mostly seen in MDS (77.7%). A study by Bhasinet al4, in 10% case were found hypolobated forms.

Immature form seen in 17% (11 cases) of thrombocytopenia in present study. Dwarf form were seen in 20% (13 cases) in present study. Bare form were seen in 6% (4 cases). 4.5 % (3 cases) show budding.

Emperipolesis was seen only case of thrombocytopenia caused by MDS. The finding of Cytoplasmic vacuolization was seen in one case of ITP.

All the findings noted in bone marrow aspiration were corroborated with finding in bone marrow biopsy.

CONCLUSION

In present study, 64 cases of bone marrow examination (thrombocytopenia) are study in Department of Pathology, SMS Medical College & Hospital are included.

In the present study, An attempt is made to elucidate the changes in megakaryocytes both numerical and morphological, causing thrombocytopenia.

This study reveals that most common cause of megakaryocytic changes causing thrombocytopenia is myelodysplastic syndrome followed by megaloblastic anemia, idiopathic thrombocytopenic purpura and others.

This study has revealed that dysplastic changes in megakaryocytes are about 81% cases of myelodysplastic syndrome and 19% cases of non myelodysplastic syndrome.

Megakaryocytic changes including dysplastic (micromegakarocyte, multiple/single separate nuclei, hypogranular form) and non dysplastic changes (hypolobated, budding, dwarf form, bare form, immature form, cytoplasmic vacuolation, emperipolesis) are required to fully understand the pathogenesis of various hematopoietic disorder. This study may be help in early diagnosis in various hematopoietic disorder.

Mere presence of dysplastic changes only should not be straight forward for diagnosis of myelodysplastic syndrome, other hematological parameters and complete clinical history is required to correlate.

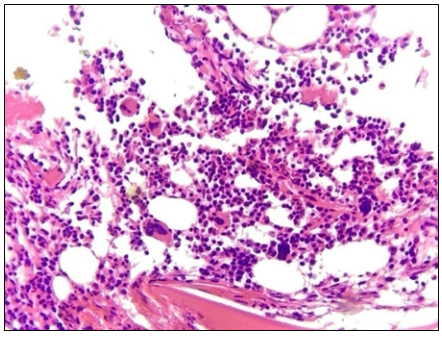

Figure1: Bone Marrow biopsy showing dysplastic megakaryocytes seen in case of myelodysplastic syndrome. (10x10)

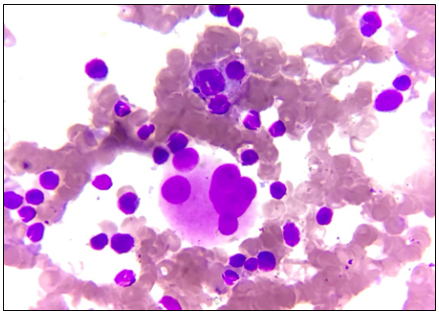

Figure2: Bone Marrow aspiration showingmegakaryocytes with multiple separate nuclei in case of myelodysplastic syndrome. (10x40)

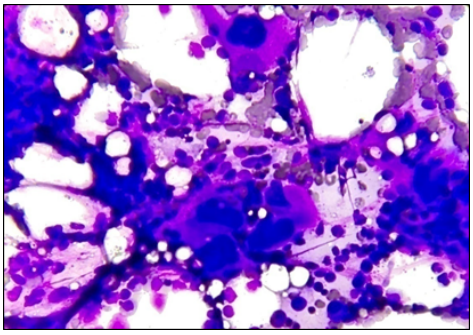

Figure 3: Bone Marrow aspiration showing megakaryocytic clusters in case of idiopathic thrombocytopenic purpura. (10x40)

Figure 4: Bone Marrow aspiration showingnormal (red arrow) and hypolobated (black arrow) megakaryocytes in background of erythroid and cells of myeloid series in megaloblastic anemia. (10x40)

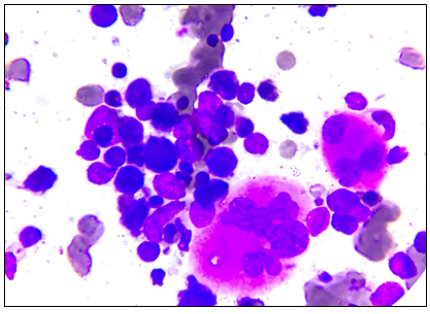

Figure 4: Bone Marrow aspiration showingnormal (red arrow) and hypolobated (black arrow) megakaryocytes in background of erythroid and cells of myeloid series in megaloblastic anemia. (10x40)

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