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A Study on Association Between Peripheral Blood Thrombocytopenia and Bone Marrow Findings

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ABSTRACT
The current study was conducted to determine the frequency of different circumstances related to low platelet count and to document the changes in megakaryocytes in different cases of thrombocytopenia. These cases were then submitted for bone marrow investigation for different reasons between March 2021 and December 2022. Slides of BMA (leishman stained) were obtained and examined. The medical information, blood tests and other important lab tests were also collected. The biopsy sample was preserved in a 10% buffered formaline solution overnight and then subjected to decalcification for 48-72 hrs, depending on the hardness of the sample, using a 15% EDTA solution. The most frequent reason for seeking a bone marrow examination in patients of thrombocytopenia was Dimorphic anaemia (24 cases, 30%). The second most frequent reason was MDS (12 cases, 15%) which was similarly followed by acute lymphocytic leukaemia (ALL) and blast crisis of chronic myeloid leukaemia (CML). Additional research on the assessment of changes in megakaryocytes and their role in thrombocytopenia can enhance our understanding of the development of various blood disorders. Megakaryocytes, thrombocytopenia, blood disorders.

INTRODUCTION

Mature MKs produce circulating platelets by developing the cytoplasmic features and functions required for platelet activity[1,2] achieving cell sizes less than 50-100 microns in diameter and ploidy levels of up to 128 N[3,4]. Endoreduplication (polyploidization) and increase in cytoplasmic volume are the characteristic features of MK maturation[5]. The generation of platelets by megakaryocytes necessitates a complex sequence of restructuring processes that lead to the liberation of numerous platelets from a solitary megakaryocyte. Dysplastic alterations are widely recognised in megakaryocytes in thrombocytopenia linked to MDS. However, they are also seen in megakaryocytes in non-myelodysplastic haematological disorders as well. However, there is limited information available on how common dysplastic changes occur in megakaryocytes in non-myelodysplastic haematological conditions. This study was conducted to gain a better understanding of the dysplastic changes in megakaryocytes and their role in causing low platelet count in disorders other than MDS. The aim was to improve the accuracy of diagnosis. Thrombocytopenia (where the number of platelets is fewer than 150,000 µL) can result in insufficient blood clotting and a higher chance of bleeding[6]. Thrombocytopenia is commonly encountered in various hematological disorders including myelodysplastic syndromes (MDS) as well as various non-myelodysplastic hematological conditions[7]. Myelodysplastic syndromes (MDS) are a diverse collection of blood illnesses caused by abnormal hematopoietic stem cells in the bone marrow (BM). These abnormalities lead to BM failure and an elevated likelihood of developing acute myeloid leukaemia (AML)[8]. Megakaryocytic changes have also been observed in certain bone marrow aspiration (BMA) studies in non-myelodysplastic diseases. The current study was conducted to determine the frequency of different circumstances related to low platelet count and to document the changes in megakaryocytes in different cases of thrombocytopenia.

MATERIALS AND METHODS

A review of 80 bone marrow aspirations was carried out at a tertiary care center that serves both urban and rural populations in West Bengal. All the instances of thrombocytopenia that were identified on the haematology analyzer (platelet count <1, 50,000) and later verified through peripheral smears were included in the study. These cases were then submitted for bone marrow investigation for different reasons between March 2021 and December 2022. Slides of BMA (leishman stained) were obtained and examined. The medical information, blood tests and other important lab tests were also collected. The biopsy sample was preserved in a 10% buffered formaline solution overnight and then subjected to decalcification for 48-72 hrs, depending on the hardness of the sample, using a 15% EDTA solution. The sample was later processed. Thin sections of 2-3 microns were cut and stained with hematoxylin and eosin, as well as additional specific stains where needed. Hypogranular forms were regarded as dysmegakaryocytopoiesis. Mature megakaryocytes were believed to possess between four and sixteen nuclear lobes. Immature megakaryocytes were described as early stages of megakaryocytes with limited bluish cytoplasm and a nucleus that occupied the majority of the cell, lacking lobulation. Dysplastic megakaryocytes were characterised as those with one or more distinct nuclei. Micromegakaryocytes were characterised as megakaryocytes that had a size similar to that of a large lymphocyte/monocyte with a single/bilobed nucleus. The megakaryocytes were regarded to exhibit platelet budding if there was budding of cytoplasmic processes from their surfaces. Hypogranular forms were described as megakaryocytes with pale grey or clear cytoplasm and few or no granules. The kind of cell observed inside the megakaryocyte in emperipolesis was also recorded. In this investigation the quantity and morphological alterations were predetermined for scoring reasons prior to the start of the trial. The count of megakaryocytes was classified as normal (one megakaryocyte per one to three low-power fields) increased (more than two megakaryocytes per low-power field) or decreased (one megakaryocyte every five to ten low-power fields)[9]. The existence of unusual megakaryocytes such as micromegakaryocytes, dysplastic forms, megakaryocytes with divided lobes and hypogranular forms, were classified as dysmegakaryocytopoiesis.

RESULTS

The most frequent reason for seeking a bone marrow examination in patients of thrombocytopenia was Dimorphic anaemia (24 cases, 30%). The second most frequent reason was MDS (12 cases, 15%) which was similarly followed by acute lymphocytic leukaemia (ALL) and blast crisis of chronic myeloid leukaemia (CML). 57% of the participants in the current study had a mild fever. Factors contributing to thrombocytopenia in the current study. Most common cause of thrombocytopenia came out to be megaloblastic anemia. As seen, megaloblastic anemia is relatively more common in females in our set up. Megakaryocytes were reduced in majority cases. Megakaryocytes of small size were observed in patients of CML. Immature shapes and leftward shift

Table 1: Condition associated with thrombocytopenia in present study

Conditions	Number	Percentage
Dimorphic anaemia	24	30.00
Myelodysplastic syndromes (MDS)	12	15
Blast crisis Chronic myeloid leukemia (CML)	08	10
Acute lymphocytic leukemia (ALL)	07	8.75
Infection associated thrombocytopenia (IAT)	04	56
Lymphocytic leukemia (CLL)	03	3.75
Idiopathic thrombocytopenic purpura (ITP)	03	3.75
Megaloblastic Anaemia	05	6.25
Multiple myeloma (MM)	02	2.5
Acute myeloid leukemia (AML)	02	2.5
Hairy cell leukemia (HCL)	03	3.75
Lymphoma spill	02	2.5
Aplastic Anaemia	01	1.25
hypersplenism (HS)	02	2.5
Bone marrow necrosis (BMN)	01	1.25
HD (post chemotherapy)	01	1.25

Table 2: Megaloblastic anemia cases age and sex distribution of megaloblastic anemia

Age groups	Male	Female	Total
0-10	3	5	8
11-20	8	10	18
21-30	7	5	12
31-50	10	8	18
Above 50	11	13	24

Table 3: Number of megakaryocytes in cases of megaloblastic anemia

Number	Cases (total 68)	Percentage
Normal	18	26.4
Increased	18	26.4
Decreased	32	47.05

were seen in the instances of ITP. Age, gender distribution, appearance and morphology of megakaryocytes in instances of MDS. All four individuals with MDS were over 50 years old. All of them had a temperature. Every patient showed a reduction in megakaryocytes in their bone marrow. Three out of the four patients had underdeveloped megakaryocytes, whereas one patient had overdeveloped megakaryocytes. Megakaryocytes were significantly decreased or not present in instances of acute leukaemia, aplastic anaemia and gelatinous marrow transformation.

DISCUSSION

MK and platelets, which are their offspring, are highly specialised cells that play a role in blood clotting and inflammation. Given that each platelet has a lifespan of around 10 days the platelet inventory is constantly replenished through the generation of new platelets from the maturation of MK[10]. Abnormal megakaryocytic proliferation and differentiation is usually observed in individuals with myelodysplastic syndromes (MDS)[11]. In this study a notable distinction was observed in the MK number between MDS and non-MDS individuals ($p = 0.017$) with a larger count being more suggestive of a non-MDS condition. The main morphological characteristic observed in all cases of ITP in this investigation was a change to younger, less developed megakaryocytes and a decrease in the number of mature megakaryocytes that produce platelets (sensitivity = 100%, specificity = 68%). Houwerzijl *et al*. made similar observations, attributing them to apoptotic and para-apoptotic forms of programmed cell death (PCD) in mature megakaryocytes. Many of the unusual megakaryocytes were encircled by neutrophils and macrophages, with some undergoing phagocytosis. Improper programmed cell death (PCD) of fully developed megakaryocytes can interfere with the production of platelets and a type of PCD similar to apoptosis, known as para-apoptosis, happens in ITP. Megaloblastic anaemia exhibits many symptoms as observed in the current study. Pale skin and lack of strength are observed in all patients. This is caused by the inadequate production of blood cells, which leads to a shorter lifespan of red blood cells and the early destruction of forming large immature cells in the bone marrow, resulting in low levels of haemoglobin. In the current study, 47 out of 76 cases (61.8%) had a low grade fever, while a study conducted by Sunil *et al*. reported that 65.5% of patients had a low grade fever. Fever was notably the most frequent cause for infection, since the individual is more prone to it because of reduced ability of neutrophils and macrophages to fight germs they eat. Megaloblastic anaemia is a significant contributor to cytopenia, which includes pancytopenia and bicytopenia. A study conducted by Sarode *et al.* found that 43.8% of cases had pancytopenia and 80.5% had bicytopenia.

CONCLUSION

Additional research on the assessment of changes in megakaryocytes and their role in thrombocytopenia can enhance our understanding of the development of various blood disorders. This knowledge may lead to wider clinical use of new approaches to control platelet levels and function.

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