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Diagnostic dilemma in hypoplastic marrow- focusing on mast cell analysis and CD34 positive cells for Aplastic anemia v/s Hypoplastic Myelodysplastic Neoplasm

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Introduction

Pancytopenia with hypocellular marrow is seen in several conditions. The most notable are aplastic anaemia (AA) and hypoplastic myelodysplastic neoplasm (hMDS). Both are primary examplifications of BM failure and have overlapping clinico-pathological features. Distinguishing between the two is pivotal. They bear different operation protocols and have distinct vaticinations(1).

Aplastic anemia is defined as pancytopenia occurring due to hypocellular marrow. In the majority of cases, the exact reason remains unknown, hence labelled as idiopathic aplastic anemia. The rest are secondary to toxins, chemotherapy, viral infections, etc. The most common identifiable cause is an autoimmune response where one's own immune system attacks the stem cells in the bone marrow, leading to suppressed hematopoiesis [2].

MDS is a group of hematologic disorders that primarily lead to ineffective hematopoiesis in the bone marrow, leading to the production of abnormal entities. Its etiology involves genetic mutations in hematopoietic stem cells, leading to defective differentiation & maturation of blood cells[3].

Hypoplastic myelodysplastic syndrome (hMDS) constitutes roughly 10–15% of all MDS cases. This entity is characterized by a hypocellular bone marrow, which is less than average age and is generally diagnosed in cases who are youngish in age as compared to other forms of MDS(4)

Bone marrow progenitor cells are the precursor, or original source, of mast cells. These precursor cells generally make up lower than 1% of all nucleated cells in the bone marrow.

The term 'AA' refers to aplastic anemia, a condition in which these cells show a relative increase because they have longer life spans and are not targeted by the

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immune system in the stem cell compartment[5,6]. 'MDS-h' stands for hypoplastic myelodysplastic syndrome. Recent studies suggest that measuring mast cell count can help distinguish AA from MDS-h, as AA generally presents with increased mast cells, whereas cases of MDS-h with increased mast cells are less common.

CD34+ hematopoietic stem cells play a central part in the pathophysiology of both AA & hMDS. They constitute around 1-2%of the bone marrow cellularity. On one hand, in AA, these cells are lower down as they become prey to their autoimmune destruction. On the other hand, in the case of hMDS, CD34+ cells are the cells from which this neoplasm originates, leading to an increase in number.

The implicit quantitative difference between CD34+ bone marrow cells in hMDS and AA suggests that they could act as a useful parameter to distinguish between the above two conditions[7,8,9,10].

The aim of the study is to assess the distribution of mast cells and CD34 cells in hypoplastic marrow and to determine their role in the differential diagnosis of aplastic anemia and hMDS.

Materials and methods

Among all cases of pancytopenia that were appertained to the Department of Pathology, SCB Medical College, 100 cases were included in this study. This was a retrospective study conducted over a 2-year period from 2023 to 2025. A detailed clinical history was taken. Ethical clearance was attained through a duly completed approval process prior to initiation of any work-up. Only hypoplastic or aplastic bone marrow biopsies that met the inclusion criteria of adequate biopsy (at least 1 cm in length & a minimum of four marrow spaces) were included, while samples with poorly preserved paraffin blocks or insufficient tissue were excluded. The H&E-stained tissue slides were meticulously examined to evaluate bone marrow cellularity and morphology, and later cases were stratified into 3 categories-

the first category of aplastic anemia(AA),

The second category of hypoplastic myelodysplastic syndrome(hMDS) and

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hypoplastic marrow attributable to other etiologies.

Special staining with toluidine blue was applied to facilitate quantification of mast cells in bone marrow. The total number of cells was calculated per 200 nucleated cells after observing 5-10 HPFs. Mast cell percentage was computed. Mast cell percentage of >1 was quantified as raised.

Immunohistochemical analysis for CD34 was conducted on paraffin-embedded formalin-fixed blocks to assess hematopoietic progenitor cell counts, which were compared across the 3 groups. The total number of positive cells was counted and assessed as <> 0.5% of the total hematopoietic cells.

All data were systematically compiled, tabulated, and analysed using standard statistical methods, with a P-value <0.05 established as the threshold for statistical significance.

RESULTS

The present study revealed a wide range of age distribution, with the majority of cases in the age group of 0-20 years (33%), while the least were seen in the 20-40 years of age (19%).

Table 1 represents the age distribution of cases.

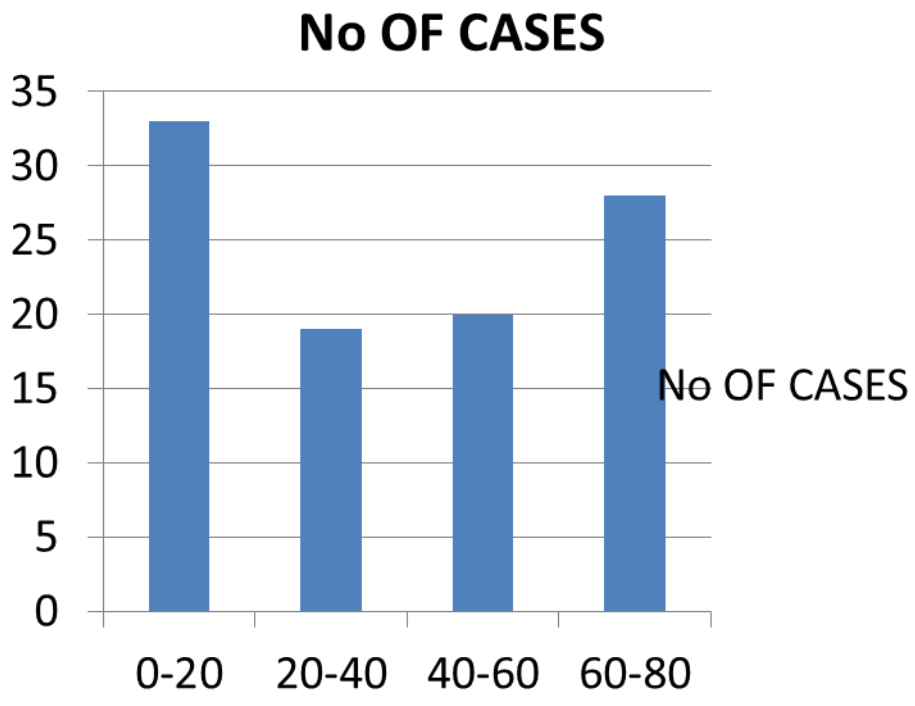

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Table 2 GENDER DISTRIBUTION OF CASES

GENDER	No O CASES
Males	64
Females	36
Total	100

Table 3: DISTRIBUTION OF CASES ACCORDING TO CLINICAL FEATURES

CLINICAL FEATURES	NO OF CASES
Fever & Weakness	50
Weakness	30
Fever , Weakness & pallor	15
Weakness & bleeding	5
Total	100

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Table – 4 MAST CELL EXPRESSION

INCREASE IN MAST CELLS	APLASTIC ANEMIA	HYPOCELLULAR MARROW	hMDS
	COUNT(%)	COUNT(%)	COUNT(%)
ABSENT	7(22)	24(50)	6(31)
PRESENT	26(78)	24(50)	13(69)
TOTAL	33	48	19

Table-5 CD34+ EXPRESSION

DIAGNOSIS	NO OF CASES	CD34+ EXPRESSION	DESCRIPTION
APLASTIC ANEMIA	33(30,3)	DECREASED	Most cases show markedly decreased number(<0.5% CD34+)
hMDS	19(16,2)	INCREASED	Most cases show clusters or preserved levels of 0f CD34+ cells (>0.5% CD34+)
HYPOCELLULAR MARROW	48	VARIABLE	CD34+ staining ranges from low to elevated.

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Among the genders, male predilection was noted with the M: F ratio being 16:9. Overall, 36%of the total population were female, and 64%of the population were male. Table 2 represents the gender distribution of cases.

Table 3 represents the distribution of cases according to clinical features, where the majority of cases(50%) presented with fever & weakness.

This study included a total of 100 cases, of which 33% cases were AA, 19% cases were hMDS, and 48% cases were diagnosed as Hypocellular marrow.

Mast cells in the Bone Marrow were highlighted using Toluidine Blue and counted among 200 nucleated cells. A count of more than 1% was considered as increased, which was seen in 63% of total cases. Increased count of mast cells was most common in AA (26,78%), followed by HM (24, 50%), and MDS-h (13, 69%). A chi-squared test showed a significant link between an increased number of mast cells and the different diseases, like AA & hMDS. (P-value 0.040). [Table - 4]

CD34 IHC expression helped calculate HSCs. If the expression was below 0.5% of all the hematopoietic cells of the marrow, it was considered decreased expression, which was noted in 33% of the cases.[Table-5]

An increased number of mast cells was seen in 63% of cases of the total study population, while significantly decreased/absent HSCs were seen in 33% cases. Among 33 cases of AA, increased mast cells were seen in 26(78%) cases, while decreased expression of CD34 was seen in 30(91%) cases. Among 19 cases of hMDS, a total of 13(69%) of the cases showed an increased number of mast cells, while 16(84%) cases showed preserved levels of 0f CD34+ cells(>0.5% CD34+)

DISCUSSION

There are several inherited and acquired conditions that present with pancytopenia along with hypocellular marrow. In the case of Patients with MDS-h, they are known to have a worse prognosis as they are more prone to neoplastic progression.

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Establishment of correct diagnosis in such a scenario is paramount as the cause of the disease significantly affects the choice of therapy.BM evaluation plays a central role in diagnosing both AA & h-MDS. They offer subtle clues that aid in diagnosis. One can appreciate trilineage atypia & presence of blasts in BMA, which indicates towards h-MDS. Special tests like IHC can confirm the presence of blasts as they are CD34 positive. However, in hypocellular marrow, lines become blurred due to the scarcity of the hematopoietic cells in the BM. Another point of conflict could be immature cells like proerythroblasts or a subset of lymphoid cells being mistaken for blasts by a pathologist.[11]

Analysis and calculation of mast cells in the BM was done by several researchers, and a common finding was that the number of mast cells was elevated in patients with AA. Our study is concordant with such studies [12]

Few studies have hypothesized that mast cells could be the cause of autoimmune attack by cytotoxic killer cells, leading to BM damage and thus suppressing hematopoiesis in AA.

According to the literature, CD34 expression of BM stem cells plays an important role in pathophysiological pathways of AA as well as hMDS.[13]

At the time of hematopoiesis, several complicated interrelations occur between the hematopoietic stem cells and the niche within which they reside in the BM. Hence, it is difficult to pinpoint the exact cause behind dysregulated hematopoiesis.

The BM microenvironment is important in maintaining the function of HSC as it is thought to transmit signals sustaining key HSC properties like regenerating capability and multilineage reproducing capacity.

Hence, it is difficult to pinpoint the exact cause behind dysregulated hematopoiesis.

In AA, CD34+ hematopoietic cells are subjected to an autoimmune attack, leading to their downfall. Whereas in the case of hMDS, the CD34+ stem cell plays a central role in its clonal proliferation. Consequently, they are elevated in hMDS. Present findings suggest that the count of CD34+ stem cells is a helpful

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method to discern between AA and hMDS, consistent with previous studies[8,13]

CONCLUSION

Aplastic anemia is characterized by raised mast cell count in the bone marrow concomitant with a fall in CD34 counts, indicative of immune dysregulation. On the contrary, hMDS exhibits fewer mast cell presence and raised CD34 cell count, reflecting abnormal hematopoiesis and dysplastic features.

The present study concludes that quantification of Mast cell & CD34 cells in the BM biopsies may serve as a supplementary tool to other diagnostic modalities to provide accurate diagnosis in cases with overlapping features. However, further research is required for a better understanding of their role in the BM microenvironment, to improve future treatment of both these conditions.

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