Hemogram And Bone Marrow Morphology In Cases Of Pancytopenia

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Citation

DOI: 10.5580/1684

Abstract

Objectives: This study was carried to identify the underlying etiopathology of pancytopenia and to find out the bone marrow morphology of aspiration smears. This study was conducted over a period of 12 months in the department of pathology. Bone marrow aspiration smears of patients fulfilling the criteria of pancytopenia and other hematological malignancies were examined. 70 cases underwent bone marrow aspiration mean age was 30 years (range 21 days to 80 years) 5 cases were children (3.5%), males 33 (23.1%), females 32 (22.4%). Male: Female ratio was 1.03:1. The commonest cause was erythroid hyperplasia seen in 28 cases (19.6%) followed by normocellular marrow in 19 cases (13%), hematological malignancies in 9 cases (6.3%) and Cryptococcus in 1 cases (0.7%). Multiple myeloma was the commonest hematological malignancy constituting 4 cases of all hematological malignancies. In children, commonest finding was normal bone marrow, while in adults erythroid hyperplasia was commonest finding followed by 9 cases of all hematological malignancies. The present study was carried out to determine the cause of pancytopenia and also establish diagnosis in other hematological malignancies. Bone marrow examination was able to establish diagnosis in 70 cases. Erythroid hyperplasia was the commonest diagnosis, followed by normocellular marrow and hematological malignancies.

INTRODUCTION

Bone marrow examination is an established diagnostic modality in the evaluation of various hematological disorders. In case of ineffective hematopoiesis the marrow may be normocellular or hypercellular (11). Bone marrow examination is extremely helpful in evaluation of pancytopenia. The presenting symptoms are attributed to the anemia or the thrombocytopenia. Leucopenia is often seen in subsequent course of the disorder (13).

Pancytopenia is defined by reduction in all three formed elements of blood below the normal reference range (11). Varieties of hematological and non-hematological disorders may affect bone marrow either primarily or secondarily, resulting in the manifestation of pancytopenia (14). The incidence of various hematological disorders causing pancytopenia varies due to geographical distribution and genetic predisposition (9). The management and prognosis of pancytopenia depends on the underlying etiopathology. Hence the finding of correct etiopathology in a given case is crucial. For this purpose, the objective of this study was to find the underlying etiopathology of pancytopenia.

METHODS AND MATERIALS

This study was carried out for 12 months in the department of pathology. A total of 70 cases of bone marrow examination were carried out on patients with peripheral blood examination revealing (32) pancytopenia, (17) microcytic hypochromic anemia, (10) normocytic normochromic blood picture, (4) multiple myeloma, (3) dimorphic anemia, (2) chronic myeloid leukemia, (1) bicytopenia and (1) leukoerythroblastic blood picture.

The criteria for pancytopenia were hemoglobin (Hb) < 10g/dl, total leucocytes count (TLC) < 4000/cumm and platelet count < 1 lakh/cumm.

Bone marrow aspiration was performed using klima needle from posterior superior iliac spine in all 70 cases and trephine biopsies was performed using jamshidhi needle in 25 cases. A complete blood count was done using hematology auto analyzer. Peripheral smear examinations were performed in all 70 cases. Iron studies were done in few cases of
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microcytic hypochromic anemia.

**EVALUATION OF SLIDES;**

The cellularity, differential counts and megakaryocytic density were done on all bone marrow samples and recorded in a proforma. They were assessed subjectively. The cellularity was graded as hypocellular, normocellular or hypercellular. Multiple areas of each slide were screened and an estimate was made. Samples were evaluated for the presence of iron, tumor staging and presence of tumor cells.

**RESULTS**

This study was carried out for 12 months in the department of pathology. The total numbers of bone marrow examination performed were 70 cases. There were 33 males, 32 females and 5 children. The male to female ratio was 1.03:1. The mean age was 30 years ranged from 21 days to 80 years. Hemogram revealed variable changes in red cell indices and red cell distribution width. Peripheral blood examination showed clumping of RBCs, immature erythroid cells in the peripheral blood with variable degree of anisopoiokilocytosis in few cases. We reported a case of autoimmune hemolytic anemia based on hemogram and peripheral smear examination, confirmed by coombs test.

Bone marrow aspiration findings and distribution of patients are shown in Table 1.

**Figure 1**

Table 1: Age Distribution of Pancytopenia Cases n=70

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>9</td>
<td>12.85%</td>
</tr>
<tr>
<td>10-20</td>
<td>5</td>
<td>7.14%</td>
</tr>
<tr>
<td>20-30</td>
<td>20</td>
<td>28.58%</td>
</tr>
<tr>
<td>31-40</td>
<td>14</td>
<td>20%</td>
</tr>
<tr>
<td>41-50</td>
<td>11</td>
<td>15.72%</td>
</tr>
<tr>
<td>51-60</td>
<td>7</td>
<td>10%</td>
</tr>
<tr>
<td>61-70</td>
<td>2</td>
<td>2.85%</td>
</tr>
<tr>
<td>&gt;70</td>
<td>2</td>
<td>2.85%</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

Of the total 70 bone marrow examined 28 were erythroid hyperplasia, 19 normocellular, 8 hypocellular and 3 megaloblastic marrow (table 2). Comparative analysis of patients of bone marrow aspiration findings in children and adult of various hematological malignancies are shown in (table 3). Hematological malignancies constituted 9 cases. Four multiple myeloma constituted (5.7%) of all hematological malignancy. Two cases of chronic myeloid leukemia. A case of ITP in pediatric age and CLL/SLL was reported in 80 year old female (table 4).

**Figure 2**

Table 2: Bone marrow aspiration finding in cases of Pancytopenia

**Figure 3**

Table 3: Comparison of bone marrow aspiration findings in children and adults
A rare case of Non secretory Multiple myeloma presenting with atypical imaging features and (>40%) atypical plasma cells was reported. Free light chain assay in conjunction with protein electrophoresis was performed for confirmation.

Diagnosis of fanconi’s anemia, and mucopolysaccharidosis was made only on clinical findings. Hematological parameters did not add any additional findings.

Table 4: Patient profile and parameters in hematological malignancies

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Acute leukemia</th>
<th>CML</th>
<th>ITP</th>
<th>CLL/SLL</th>
<th>Multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30</td>
<td>30-35</td>
<td>4</td>
<td>80</td>
<td>23-73</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>5.8</td>
<td>5.9</td>
<td>8</td>
<td>9.8</td>
<td>4.7-11</td>
</tr>
<tr>
<td>TLC (per mm3)</td>
<td>1000</td>
<td>1.2-2.3 lakhs</td>
<td>8000</td>
<td>40000</td>
<td>4700-13000</td>
</tr>
<tr>
<td>Platelet (per mm3)</td>
<td>630000</td>
<td>2.3-3 lakhs</td>
<td>40000</td>
<td>90000</td>
<td>1.76-6.5 lakhs</td>
</tr>
</tbody>
</table>

Figure 4

Figure 6

Fig 1: Bone marrow showing dysmegakaryopoiesis in Megaloblastic anemia (Giemsa, x 1000).

Fig 2: Bone marrow showing dyserythropoiesis in Megaloblastic anemia (Giemsa, x 1000).

Figure 7

Fig 3: Bone marrow showing islands of lymphoid cells in CLL/ SLL (Giemsa, x 1000).
Hemogram and bone marrow morphology in cases of pancytopenia

**Figure 8**
Fig 4: Bone marrow showing binucleate and uninucleate plasma cells in MM (Giemsa, x 1000).

**Figure 10**
Fig 6: Bone marrow showing hypocellular area with increased fat space in Aplastic anemia (H&E, x400)

**Figure 9**
Fig 5: Bone marrow showing erythroid hyperplasia (Giemsa, x 1000).

**Figure 11**
Fig 7: Bone marrow showing giant megakaryocyte (Giemsa, x 1000).

**DISCUSSION**
Hemogram and bone marrow examination for the evaluation of various hematological disorders is frequently requested by clinicians. In the present study 70 cases were evaluated to rule out pancytopenia and other hematological disorders. Out of 70 cases 32 were reported as pancytopenia, 17 were microcytic hypochromic anemia, 10 normocytic normochromic blood picture, 3 dimorphic anemia, 2 bicytopenia, 2 CML, 1 CLL, 1 case of leukoerythroblastic blood picture was diagnosed on peripheral blood.

Hemogram showing high MCHC, RDW and corrected reticulocyte count can give us a clue to certain type of hemolytic anemia and necessitate critical evaluation of
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peripheral smear to reach a definitive diagnosis.

The typically pancytopenic presentation combined with megaloblastic dyspoiesis in bone marrow can be interpreted mistakenly as primary myelodysplasia and present as a challenging differential diagnosis. Vit B12 deficiency in a mother with undiagnosed pernicious anemia had features of infantile monozomy seven syndrome. There was a profound anemia and leukoerythroblastic reaction, the bone marrow showed trilineage dysplasia with multinucleated and megaloblastic erythroid precursors. Low platelet count (<40x10^9/micro lit [<40x10^9] L] and fetal hemoglobin level (>10%) has been used as prognostic scoring device \(^{(18)}\).

Clinically it is difficult to distinguish chronic aplastic anemia (CAA) from myelodysplastic syndrome (MDS). As prognosis and treatment of CAA and MDS are different it is extremely important to make a differential diagnosis for the two diseases. The mean cell counts of monocytes and platelets in peripheral blood of CAA patients significantly lower than those of MDS patients. Decreased blood cell counts with decrease in bone marrow cellularity without dyshematopoiesis in CAA patients. Peripheral blood monocytes, fibrous tissue and cellularity in bone marrow are increased in MDS \(^{(22, 23)}\). In our study aplastic anemia was diagnosed in a 15 year old female with history of menorrhagia. Peripheral smear examination revealed pancytopenia and bone marrow showing hypocellular areas with increased fat space and fibrosis.

Anemia is the most common hematological abnormality in HIV sero positive patients. Neutropenia is common in advance stages of AIDS. Thrombocytopenia is known to be frequent complication of HIV \(^{(19, 21)}\).

In a study conducted by Jha et al, provided specific diagnosis in 77% of cases, commonest bone marrow findings was hypoplastic anemia(29.05%) followed by megaloblastic anemia (23.64%)\(^{(1)}\).

Comparative analysis of first and second most common cause of pancytopenia is shown in (table5). In the present study bone marrow aspiration provided specific diagnosis in 70 cases. Erythroid hyperplasia, 28 of 70 cases (40%) was the commonest diagnosis in the present study and its relationship to pancytopenia is uncertain. Second most commonest diagnosis was normocellular marrow (27.14%).

Figure 12
Table 5: A comparison of the first and second most common causes of pancytopenia in different studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>No. of cases</th>
<th>Commonest cause</th>
<th>Second most common cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>International agranulocytosis and Aplastic anemia study group</td>
<td>Israel &amp; Europe</td>
<td>1987</td>
<td>319</td>
<td>Hypoplastic anemia (52.7%)</td>
<td>MDS (4.5%)</td>
</tr>
<tr>
<td>Keim and Ortiz</td>
<td>Israel &amp; Europe</td>
<td>1990</td>
<td>100</td>
<td>Neoplastic disease, radiation (32%)</td>
<td>Hypoplastic anemia (19%)</td>
</tr>
<tr>
<td>Hossain et al</td>
<td>Bangladesh</td>
<td>1992</td>
<td>50</td>
<td>Hypoplastic anemia (40.5%)</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>Venna and Dash</td>
<td>India</td>
<td>1992</td>
<td>202</td>
<td>Hypoplastic anemia (68%)</td>
<td>Megaloblastic anemia (23.26%)</td>
</tr>
<tr>
<td>Tilak and Jain</td>
<td>India</td>
<td>1999</td>
<td>77</td>
<td>Megaloblastic anemia (69%)</td>
<td>Hypoplastic anemia (7.7%)</td>
</tr>
<tr>
<td>Kumar et al</td>
<td>India</td>
<td>1999</td>
<td>166</td>
<td>Hypoplastic anemia (79.51%)</td>
<td>Megaloblastic anemia (14%)</td>
</tr>
<tr>
<td>Khodke et al</td>
<td>India</td>
<td>2000</td>
<td>50</td>
<td>Hypoplastic anemia (54%)</td>
<td>Megaloblastic anemia (14%)</td>
</tr>
<tr>
<td>Bajracharya et al</td>
<td>Nepal</td>
<td>2005</td>
<td>10</td>
<td>Hypoplastic anemia (59.05%)</td>
<td>Megaloblastic anemia (23.64%)</td>
</tr>
<tr>
<td>Jha et al</td>
<td>India</td>
<td>2007</td>
<td>148</td>
<td>Hypoplastic anemia (59.05%)</td>
<td>Megaloblastic anemia (23.64%)</td>
</tr>
<tr>
<td>Present study</td>
<td>India</td>
<td>2010</td>
<td>70</td>
<td>Erythroid hyperplasia (49%)</td>
<td>Normocellular (27.14%)</td>
</tr>
</tbody>
</table>

Hypercellular or normocellular marrow in cases of pancytopenia can also be seen in cases with ineffective hematopoiesis with cell death within the marrow \(^{(10)}\).

Megaloblastic anemia was the common diagnosis in other...
In our study only 3 cases of megaloblastic anemia (4.2%) was identified. In all 3 cases hemogram and peripheral smear showed pancytopenia. Bone marrow aspiration showed megaloblastic change in all three lineages of cells. In treated cases the bone marrow aspiration smears revealed early normoblastic maturation with megaloblastic features. Similarly, hypercellular marrow in the presence of peripheral pancytopenia can be a manifestation of paraneoplastic syndrome (11).

Hypocellular marrow was seen in only one case underlying exposure to myelotoxic drug (chlorpromazine). The frequency of various diagnostic entities causing pancytopenia has been attributed to differences in the methodology and stringency of diagnostic criteria, geographic difference and underlying exposure to myelotoxic drugs (7).

Cryptococcus was seen in only one case in contrast to other studies.

The most common hematological malignancy was multiple myeloma constituted 4 out of 70 cases. Plasmablastic variant of multiple myeloma with type 2 diabetes mellitus and grade 3 renal disease and a single case of NSMM with atypical presentation was studied in contrast to the other studies.

Acute leukemia, ITP were the only two malignancies in children while plasma cell myeloma, NHL and CML were the hematological malignancies encountered in adults. Acute leukemia alone constituted (19.59%) of total cases of pancytopenia in the study by Jha et al (1). In our study acute leukemia constituted (1.4%). Similarly in studies conducted by Khodke et al and Tilak et al one cases of AML was detected as the cause of pancytopenia (3,4). Similarly, acute leukemia was the third common cause of pancytopenia in the study by Varma and Dash (8). In contrast to the study by Kumar et al where no acute leukemia was detected (9).

Few rare but interesting cause of pancytopenia includes fancies’ anaemia and mucopolysaccharidosis. Bone marrow examination did not show considerable finding in these patients and were kept under follow up.

Despite the use of genetics, molecular biology and immunology for the diagnosis, routine hemogram and bone marrow examination still cannot be replaced.

CONCLUSION

Our study shows that Hemogram and bone marrow examination are of equal value in vast majority of cases. Bone marrow aspiration and biopsy both need to be provided. In the present study, bone marrow aspiration was able to establish the diagnosis in 70 cases. Hematological parameters was of little value in diagnosis of rare cases like NSMM, fancies anaemia, and mucopolysaccharidosis, which required additional tests. Proper diagnostic work up is essential before use of hematinics and blood transfusion in all patients presenting as pancytopenia. Limitations of this study include lack of facilities and financial constraints.

Hemogram and bone marrow examination necessitate critical evaluation of hematological disorders to reach a definitive diagnosis. Emphasizing the importance of systematic and meticulous examination of hemogram to render definitive diagnosis is necessary. Diagnostic clues obtained from hemogram and bone marrow examination was useful in early diagnosis of disease and had better prognosis in majority of cases.

References

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