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**Original Research Article**

# Evaluation of haematological findings in cases of pancytopenia

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## ABSTRACT

**Background:** Pancytopenia is a clinical condition which poses diagnostic challenge to the haematologist. The aetiology of pancytopenia is varied and depends on many factors. A bone marrow study is highly indicated in cases of pancytopenia and it provides information regarding the underlying disease process. This study was done to learn the causes of pancytopenia and to document how each case was evaluated and followed up.
**Methods:** The present study is a descriptive retrospective one year study on bone marrow samples received in the laboratory. Bone marrow samples included aspirate smears, imprint and trephine and their findings were correlated to arrive at a final diagnosis.
**Results:** Out of the total 28 patients with pancytopenia, 35.71% were from the age group between 61 and 80 years. A male female ratio of 1.5:1 was observed. Most common presenting complaint documented was easy fatiguability. Anisocytosis with macrocytes and ovalocytes were the most common peripheral smear finding. In current study, a cellular marrow was described in 24 (85.71%) cases and hypocellularity in two (7.14%) cases. Final diagnosis was evident in 16 cases, in which the most common cause was acute leukaemia (14.28%) followed by lymphoma infiltration and myelodysplastic syndromes in 3 cases (10.71%).
**Conclusions:** Bone marrow study helps to arrive at a diagnosis of pancytopenia. But proper technique for sampling, good clinical workup and history taking and clinico haematological correlation is mandatory for the proper diagnosis of a pancytopenia case.

**Keywords:** Pancytopenia, Megaloblastoid marrow, Bone marrow study, Dyserythropoesis

## INTRODUCTION

Pancytopenia is a clinical condition, with simultaneous presence of anaemia, leukopenia and thrombocytopenia. It is not a disease entity by itself and is diagnosed in an adult, when there is reduction in the levels of haemoglobin, total leucocyte count and platelet count. It affects both sexes and all age groups. It is manifested in a wide range of disease conditions and poses a diagnostic challenge to the haematologist. An early diagnosis of the disease process and timely intervention is absolute necessary in conditions of pancytopenia.

The clinical symptoms of the patient can either be due to pancytopenia per se or due to the underlying cause. It should be suspected on clinical grounds when a patient presents with pallor, prolonged fever and a tendency to bleed but the common presenting symptoms are usually due to anaemia and thrombocytopenia.[1]

The aetiology of pancytopenia varies in different populations depending on the differences in age patterns, nutritional status, other concomitant illnesses, drug intake, climate and the prevalence of infections. Therefore, extensive evaluation of each case by proper history taking and investigations are essential for the

correct diagnosis of the underlying cause. On general examination the presence of fever, bone pain, recent weight loss, reduction in appetite, pruritus, hepatosplenomegaly can direct the clinician to the cause of the condition.[1]

A bone marrow study is highly indicated in all cases of pancytopenia and a careful examination of peripheral blood film is a forerunner which gives a lead to the aetiology. Bone marrow study includes bone marrow aspiration and trephine. Both these investigations can be done in the same setting and are usually supplementary. B.J. Bane describes the rationale of doing a bone marrow study with trephine in cases of pancytopenia.[2]

There are several works on pancytopenia from different parts of the world which report varied causes with newer entities being recognized. The present study is aimed to document in detail the step by step process in the diagnosis of pancytopenia cases and the common difficulties encountered.[3-5]

## METHODS

The present study was a descriptive retrospective study conducted in Government TD medical college, Alleppey, Kerala. Bone marrow samples which were received in the Haematology laboratory during a one year period from January 2019 to December 2019 were analysed. The patients included people of both sexes in all age groups. Case selection was based on the laboratory findings of haemoglobin level less than 13.5 g/dl in males or 11.5 g/dl in females, leucocyte count below $4x10^9$/L and platelet count below $150x10^9$/L.[1] Patients receiving chemotherapy/radiotherapy were excluded from the study.

The clinical details of the patients were collected from the medical records. Bone marrow samples which included aspirate smears imprint and trephine biopsies were assessed separately and the findings correlated to arrive at a final opinion about the bone marrow status. Statistical analysis was done using SPSS version 20.

The bone marrow samples were accompanied by peripheral smears and complete blood count results. The complete blood count included haemoglobin, haematocrit, blood cell indices like MCV, MCH, MCHC, RDW etc. The peripheral smears and bone marrow aspirate samples were stained with Leishman stain. The bone marrow trephine samples were received in neutral buffered formalin solution. A reticulocyte count was done using supravital stain when smears showed plenty of polychromatic cells.

## RESULTS

A total number of 28 patients were diagnosed to have pancytopenia in a one year period. There were 15 Males and 13 females and the patients were from all age groups from 7 years to 80 years. The most common age group was between 61 and 80 years (35%). There were 6 patients below the age of 20 years Table 1.

**Table 1: Distribution of pancytopenia cases in different age groups.**

| Age (years) | N (%) |
|---|---|
| **1-20** | 6 (21.45) |
| **21-40** | 3 (10.71) |
| **41-60** | 9 (32.14) |
| **61-80** | 10 (35.71) |
| **>81** | - |

The most common presenting complaint documented was easy fatiguability followed closely by fever. While no details were given in 6 cases, in 3 cases, pancytopenia was noted after a routine blood check-up. The list of clinical features is documented in Table 2.

**Table 2: Presenting complaints in pancytopenia.**

| Presenting complaints | N (%) |
|---|---|
| **Fever** | 5 (17.85) |
| **Fatiguability** | 7 (25) |
| **Bleeding** | 2 (7.14) |
| **Pallor** | 4 (14.28) |
| **Abdominal swelling** | 1 (3.57) |
| **No complaints** | 3 (10.71) |
| **Not documented** | 6 (21.42) |

The detailed peripheral smear showed anisocytic red cells in 22 cases. Among this, macrocytes and ovalocytes were noted in 14 cases. Normocytic normochromic anaemia was documented in 5 cases and Macrocytic anaemia in one case respectively. Nucleated RBC was noted in two cases. The list of red blood cell morphology seen in peripheral smear is given in Table 3.

**Table 3: The peripheral smear findings in pancytopenic cases.**

| Peripheral smear findings of RBCs | N (%) |
|---|---|
| **Anisopoikilocytosis** | 8 (28.57) |
| **Anisocytosis with macrocytes/ ovalocytes** | 14 (50) |
| **Normocytic normochromic** | 5 (17.85) |
| **Macrocytic anemia** | 1 (3.57) |

A predominance of lymphocytes was noted in 18 cases. Hyper segmented neutrophils were noticed in two cases, which showed megaloblastoid erythrocytes in the bone marrow aspirate. Atypical cells with increased nuclear cytoplasmic ratio were noted in three cases

In bone marrow examination, initially the cellularity is assessed. In the present study, bone marrow picture

showed a cellular marrow in 24 cases and hypocellularity in two cases.

Cellular aspirate with erythroid hyperplasia was seen in ten cases. In these megaloblastic features were seen in eight cases. Mononuclear cell population with increased nuclear cytoplasmic ratio were noted in seven cases all of which were later diagnosed as acute leukemia or bone marrow infiltration of lymphoma. Dysplastic features in more than one hemopoietic cell line were noted in two cases. Several morphological changes like micro megakaryocytes and hypo lobated megakaryocytes were noted in few cases. Mild plasma cell proliferations were documented in two cases. These above-mentioned features were seen in various combinations. The bone marrow aspirate picture in cases of pancytopenia is depicted in Table 4.

**Table 4: Bone marrow aspirate picture in pancytopenia cases.**

| Bone marrow cellularity | N | Further marrow morphology with no. of cases |
|---|---|---|
| **Inadequate** | 2 | --- |
| **Hypocellular marrow** | 2 | Fibrosis; grade 3, 1 |
| | | Marrow infiltration, 1 |
| **Cellular marrow** | 24 | Normal marrow appearance, 4 |
| | | Erythroid hyperplasia, 10 |
| | | With megaloblastoid maturation, 2 |
| | | Megaloblastoid erythroid maturation with dyserythropoesis, 6 |
| | | Increase in plasma cells, 3 |
| | | Acute leukemia/lymphoma,7 |
| | | Dysplastic features in >1 cell line, 2 |

In five cases bone marrow trephine was not done and in one case the sample was inadequate. Trephine biopsy was helpful in one case where aspiration yielded no material. The trephine biopsy sections helped in studying the architecture and pattern of marrow infiltration. In 22 cases, trephine biopsy findings correlated well with the bone marrow aspirate findings.

Streaming of cells was noted in four cases which was confirmed and graded with reticulin special stain. In 2 cases there was grade 3 fibrosis and grade 1 fibrosis in 2 cases. and Immunohistochemistry was performed in eight cases for various reasons. The outcome and utility of bone marrow trephine samples is shown in Table 5.

As shown in Table 6, final diagnosis was arrived in 16 cases in which the most common diagnosis was acute leukaemia (14.28%). lymphoma infiltration and myelodysplastic syndrome followed closely behind with three cases (10.71%) each. Only 3.57% cases of pancytopenia were due to plasma cell dyscrasia. Rare conditions like PNH, myelofibrosis and hypersplenism were also noted in 3.57% cases each.

**Table 5: Utility of trephine biopsy in different cases.**

| Outcome of trephine | N | Use of the trephine |
|---|---|---|
| **Inadequate trephine** | 1 | --- |
| **Well correlation** | 22 | IHC in cases of leukemia, 5<br>Plasma cell IHC, 3<br>Fibrosis grading (reticulin), 3 |
| **Not done** | 5 | --- |

Acute leukaemia was diagnosed in four cases of which two of the patients were below 10 years. These patients presented with cervical lymphadenopathy and bleeding diathesis. The other two were 17 years and 65 years old. All of them showed anisopoikilocytosis in smear. Three out of four cases showed atypical cells with increased nuclear cytoplasmic ration in the peripheral smears. Cells with increased nuclear cytoplasmic ratio and open chromatin were noted in the aspirate. Special cytochemistry helped in the diagnosis. Marrow infiltration was seen in 3 cases of which one patient gave history of a previous ovarian neoplasm.

**Table 6: Distribution of pancytopenia cases with their final diagnosis.**

| Final Diagnosis | N (%) |
|---|---|
| **Acute leukemia** | 4 (14.28) |
| **Lymphoma infiltration** | 3 (10.71) |
| **Megaloblastic anemia** | 2 (7.14) |
| **MDS** | 3 (10.71) |
| **Plasma cell dyscrasias** | 1 (3.57) |
| **Myelofibrosis** | 1 (3.57) |
| **Hypersplenism** | 1 (3.57) |
| **PNH** | 1 (3.57) |
| **Needs more workup** | 10 (35.71) |
| **Inadequate sample** | 2 (7.14) |

## DISCUSSION

From a total of 241 bone marrow study cases received during the study period, 28 cases satisfied the criteria for a diagnosis of pancytopenia. The most common presenting complaint documented was fatiguability which was similar to many other previous studies.[6-8,10] The second most common complaint was fever.

In the present study, there were patients from an age group range of 7 to 80 years. Maximum cases were from 61-80 years i.e. 35.71%. Previous studies on pancytopenia report different age group predilection with recent studies from Pune and Delhi showing maximum number of cases in the second decade.[2,8] Meanwhile

studies from Kashmir and Baluchistan reported more cases from >40 years of age.[9,10]

A Male to female ratio of 1.5:1 was observed in the present study. Previous similar studies also showed a similar sex ratio.[6,9] But a study by Jyotsana et al gives a female preponderance.[8]

Bone marrow aspirate sample of three cases were inadequate. However, the subsequent trephine biopsy helped the diagnosis in one of them. In 4 other cases the aspirate had scanty particles with marrow blood. Two of these cases were further diagnosed as acute leukaemia by trephine biopsy. These observations stress the importance of adhering to correct sampling techniques and the importance of doing a trephine biopsy along with aspiration.

The most frequent peripheral smear picture was anisocytosis with macrocytes or ovalocytes (50%). It was followed by anisopoikilocytosis in 28.5% cases. A single case showed predominant macrocytes in smear.

It should be concluded that macrocytes in smear could have been due to several reasons. The serum B12 levels were correlated and megaloblastic anaemia due to nutritional deficiency was diagnosed in only two cases. As explained in literature, most common cause of macrocytes could be due to erythroid hyperplasia with reticulocytosis.[1]

Erythroid hyperplasia with normoblastic maturation was noted in two cases. Since the patients were having severe anaemia, the hyperplasia of the marrow was expected. No other abnormal findings were noted in these cases.

Two patients had a low B12 levels along with megaloblastioid erythroid maturation. One among this also showed hyper segmented neutrophils in the smear. These cases were diagnosed as megaloblastic anaemia due to nutritional deficiency of vitamin B12 and treated accordingly.

Features of dyserythropoesis with megaloblastoid maturation were noted in 6 cases. B12 levels were within normal limits in few of these cases dyserythropoetic features included binucleation of erythroid precursors, fraying of the cytoplasmic borders, karyorrhexis etc. In one such patient, on further workup, an abnormal PNH clone was identified by flowcytometry. Contrary to the usual hypoplasia expected in bone marrow of PNH patients.[10] this patient showed a cellular marrow with erythroid hyperplasia and dyserythropoesiss. This patient had folate deficiency and the haemolytic picture became more evident when the folate deficiency was corrected.

Myelodysplastic syndrome was suggested in two other cases which showed additional dysplastic features in megakaryocyte series. These patients were put under strict clinical follow up.

Four cases of acute leukaemia were diagnosed from bone marrow study. These patients had cellular marrow. The natures of the monotonous population of cells were revealed by immunohistochemical stains on trephine serials. Cellular marrow of normal hemopoietic cell lines was noted in 4 cases. Hypersplenism was suggested in one such case which presented with splenomegaly.

The clinical details of the patients were insufficient in many of our cases. The lack of details regarding diet intake, drug history etc hindered further follow up of many cases. Another limitation of the present study was the inadequacy of a few bone marrow samples. It was difficult to assess the hypoplasia of the marrow due to paucity of particles. Moreover, a study with larger sample size would provide better light to the subject.

## CONCLUSION

With a detailed clinical history, physical examination and good sampling techniques, bone marrow study helps in the diagnosis of pancytopenia. Adequacy of the aspirate and the trephine should be ascertained with care. Other investigations needed for the correct diagnosis should also be performed to arrive at a final diagnosis. Cases with megaloblastic picture and dysplastic features should be followed up strictly by closely monitoring the clinical condition of the patient. A collective combined effort from the haematologist and pathologist is greatly recommended in this context.

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