Pancytopenia: A Clinico Hematological Study

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ABSTRACT

Background: Pancytopenia is a relatively common hematological entity. It is a striking feature of many serious and life-threatening illnesses, ranging from simple drug-induced bone marrow hypoplasia, megaloblastic anemia to fatal bone marrow aplasias and leukemias. The severity of pancytopenia and the underlying pathology determine the management and prognosis. Thus, identification of the correct cause will help in implementing appropriate therapy.

Objectives: To study the clinical presentations in pancytopenia due to various causes; and to evaluate hematological parameters, including bone marrow aspiration.

Materials and Methods: It was a prospective study, and 104 pancytopenic patients were evaluated clinically, along with hematological parameters and bone marrow aspiration in Hematology Unit, Department of Pathology, JJMMC, Davanagere, during the period of September 2005 to September 2007.

Results: Among 104 cases studied, age of patients ranged from 2 to 80 years with a mean age of 41 years, and male predominance. Most of the patients presented with generalized weakness and fever. The commonest physical finding was pallor, followed by splenomegaly and hepatomegaly. Dimorphic anemia was the predominant blood picture. Bone marrow aspiration was conclusive in all cases. The commonest marrow finding was hypercellularity with megaloblastic erythropoiesis. The commonest cause for pancytopenia was megaloblastic anemia (74.04%), followed by aplastic anemia (18.26%).

Conclusion: The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding disease process and to diagnose or to rule out the causes of cytopenia. These are also helpful in planning further investigations and management.

Keywords: Bone marrow aspiration, megaloblastic anemia, pancytopenia

INTRODUCTION

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice. There are varying trends in its clinical pattern, treatment modalities, and outcome. It is a disorder in which all three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number. It is not a disease entity but a triad of findings that may result from a number of disease processes – primarily or secondarily involving the bone marrow. The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients. In India, the causes of pancytopenia are not well defined, so the present study has been undertaken to evaluate the various causes and to correlate the peripheral blood findings with bone marrow aspirate. Thereby, this data would help in planning the diagnostic and therapeutic approach in patients with pancytopenia.

MATERIALS AND METHODS

The present prospective study was undertaken for a period of 2 years, from September 2005 to September 2007, at Hematology Unit, Department of Pathology, JJ.M. Medical College, Davanagere. Patients of all age groups and both sexes were included. Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood
counts for hemoglobin, leukocytes and platelets. Inclusion criteria were presence of all 3 of the following: hemoglobin, <9 g/dL; total leukocyte count (TLC), <4,000 / µL; platelet count, <100,000/ µL. Patients on myelotoxic chemotherapy were excluded. Two milliliters of EDTA (ethylene diamine tetra-acetic acid) anticoagulated blood was collected and processed through ABX MICROS 60 automated hematology analyzer; and 9 hematological parameters were obtained, which included hemoglobin, red blood cell count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV). Erythrocyte sedimentation rate (ESR) was estimated in all cases by Westergren’s method. Peripheral smear was stained by Leishman stain for all the cases and examined in detail. Bone marrow aspiration was subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian.

RESULTS

A total of 104 patients who presented with pancytopenia were studied. They consisted of 57 males and 47 females with a male-to-female ratio of 1.2:1. The age of patients ranged from 2 to 80 years (mean age, 41 years). Out of 104 cases, pancytopenia was observed in 31 pediatric patients (2-18 years); they consisted of 13 males and 18 females. No familial disease was observed in association with pancytopenia. Presenting complaints and physical findings are shown in Table 1.

The commonest mode of presentation was generalized weakness; other main symptoms were dyspnea, fever, weight loss. Pallor was noted in all cases.

Splenomegaly and hepatomegaly were seen in cases of megaloblastic anemia, followed by subleukemic leukemia and malaria. Bony tenderness was seen in multiple myeloma. Lymphadenopathy was noted in subleukemic leukemia – lymphoblast type.

Hematological parameters in the 3 subgroups of pancytopenia are shown in Table 2.

The predominant blood picture was dimorphic anemia (37.5%), followed by macrocytic anemia (31.7%); peripheral smear showed macro-ovalocytes with hypersegmented neutrophils [Figure 1]. Normocytic normochromic anemia constituted 15.3% of the cases; and normocytic hypochromic anemia, 15.3%. Leucopenia and thrombocytopenia were seen in all cases.

The causes of pancytopenia and case distribution are shown in Table 3.

Megaloblastic anemia was observed in 43 males and 34 females, their age ranging from 4 to 80 years, with a mean age of 42 years. Four patients had evidence of malabsorption syndrome. Six patients had clinical neurological deficits: subacute combined degeneration (SACD) of spinal cord in 4 and sensory ataxia in 2 patients. In the remaining 67 cases, the underlying disorder could not be established. Since B<sub>12</sub> and folate levels could not be estimated as a routine, both folic acid and parenteral hydroxycobalamine therapies were administered to all, and they showed complete clinical and hematological remission. Bone marrow aspiration showed megaloblastic erythroid hyperplasia. Megaloblasts had the characteristic feature of

| S. no. | Presenting complaints and physical findings | No. of cases | Percentage |
|-------|-------------------------------------------|-------------|------------|
| 1     | Generalized weakness                       | 104         | 100        |
| 2     | Dyspnea                                   | 45          | 43.26      |
| 3     | Fever                                     | 40          | 38.46      |
| 4     | Bleeding manifestation                     | 4           | 3.84       |
| 5     | Weight loss                               | 4           | 3.84       |
| 6     | Chills and rigor                           | 3           | 2.80       |
| 7     | Pallor                                    | 104         | 100        |
| 8     | Splenomegaly                              | 37          | 35.57      |
| 9     | Hepatomegaly                              | 29          | 26.92      |
| 10    | Jaundice                                  | 4           | 3.82       |
| 11    | Bony tenderness                           | 1           | 0.96       |
| 12    | Lymphadenopathy                           | 1           | 0.96       |

| Parameters | Megaloblastic anemia | Aplastic anemia | Subleukemic leukemia |
|------------|----------------------|----------------|----------------------|
| Hb (g/dL)  | 1.8-9.2              | 2-8.6          | 2.8-6                |
| TLC (µL)   | 500-3,900            | 700-3,800      | 600-3,200            |
| Platelets (µL) | 12,000-95,000 | 10,000-92,000 | 15,000-85,000       |

| S. no. | Causes            | No. of cases | Percentage |
|--------|-------------------|--------------|------------|
| 1      | Megaloblastic anemia  | 77           | 74.04      |
| 2      | Aplastic anemia    | 19           | 18.26      |
| 3      | Subleukemic leukemia | 4           | 3.85       |
| 4      | Malaria            | 2            | 1.93       |
| 5      | Multiple myeloma   | 1            | 0.96       |
| 6      | Storage disorder   | 1            | 0.96       |
| Total  |                    | 104          | 100        |
sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm with cytoplasmic blebs [Figure 2]. Giant metamyelocytes and band forms were predominant in granulocyte series.

Aplastic anemia was seen in 10 males and 9 females; their age ranged from 2 to 50 years, with a mean age of 26 years. In the present study, out of 19 cases of bone marrow hypoplasia, cause was not known in 16 cases and was grouped under idiopathic bone marrow hypoplasia. One patient had history of hepatitis infection. Another patient gave history of treatment with carbamazepine for epilepsy. One patient, a known case of hyperthyroidism, was on antithyroid medication. Bone marrow (BM) showed hypocellularity with suppression of erythropoiesis, myelopoiesis and megakaryopoiesis with relative lymphoplasmacytosis [Figure 3].

We encountered 4 patients of subleukemic leukemia; their age ranged from 4 to 30 years. Three cases were of AML-M2 (acute myeloblastic leukemia) and 1 case was of ALL-L2 (acute lymphoblastic leukemia). Bone marrow was hypercellular in all cases. Erythroid and megakaryocytic series were reduced. Majority of cells were myeloblasts and lymphoblasts, constituting more than 40% and 30% of cells in marrow, respectively. Bone marrow aspirate showed myeloblasts with Auer rods [Figure 4]. Malarial infestation was seen in 2 male patients aged 5 years and 25 years. Peripheral blood picture showed pancytopenia, and gametocytes of plasmodium falciparum were seen in blood smear in both cases [Figure 5]. BM was hypercellular with megaloblastic change. No malarial parasites were seen on bone marrow smears. The patients recovered after antimalarial treatment and folic acid therapy. Multiple myeloma was diagnosed in a 41-year-old female, who presented with weakness and bony tenderness. BM showed abnormal proliferation of plasma cells, constituting >40% of marrow cells, including good number of binucleate and trinucleate forms [Figure 6].

We encountered 1 case of storage disorder in a 15-year-old male, who presented with fever, pallor, hepatosplenomegaly. BM showed good number of large cells with peripherally placed relatively small nucleus and abundant multivacuolated foamy cytoplasm and was PAS (periodic acid Schiff) negative. Hence diagnosis of Niemann-Pick disease was considered.

**DISCUSSION**

A total of 104 cases of pancytopenia were studied. Age, gender-wise incidence, presenting complaints, peripheral blood picture, bone marrow aspiration smears and various causes of pancytopenia were studied in all cases, and observations were compared with those in studies published in the literature.

The age of the patients ranged from 2 to 80 years, with a mean age of 42 years. Cytopenias were observed more in males (54.81%) than females (45.19%), with male-to-female (M: F) ratio of 1.2: 1. Age and sex distribution was compared with other studies as shown in Table 4.

**Chronic lymphocytic leukemia/Small lymphocytic lymphoma**

The most common presenting complaint in our study was generalized weakness (100%), followed by dyspnea (43.26%). The most common physical finding was pallor (100%), followed by splenomegaly (35.57%) and hepatomegaly (26.92%).

The presenting symptoms were usually attributed to anemia or thrombocytopenia. Leucopenia was an uncommon cause of the initial presentation of the patient but can become the most serious threat to life during the course of the disorder. Physical findings were comparable with those in other studies as shown in Table 5.

**Hemoglobin, total leucocyte count and platelet count were comparable with those in other studies as shown in Table 6.**

Hypersegmented neutrophils were noted in 51.35% of cases compared to 84.9% in Tilak V et al. study, and Khunger JM et al. demonstrated no hypersegmented neutrophils in megaloblastic anemia. Also, relative lymphocytosis in aplastic anemia was noted in 52.63% of the cases in our study compared to 50% in Tilak V et al. study and 85.71% in Khunger JM et al. study.[4,6] Table 7 shows comparison of peripheral blood findings with other studies.

In our study, we came across 31 pediatric pancytopenic cases; again megaloblastic anemia was the common cause for pancytopenia, followed by aplastic anemia. Similar results were reported by Bhatnagar et al.[8] However, in a study by Gupta and colleagues, 105 patients aged 1.5 to 18 years, with a mean age of 8.6 years, were included in the study. Aplastic anemia was the most common cause of pancytopenia (43%), followed by acute leukemia (25%). Infections were the third most common cause of pancytopenia, of which kala-azar was the most common. Megaloblastic anemia was seen in 6.7% of the patients.[9]

In another study, 64 children were identified with diagnosis
of pancytopenia. The most common cases were infectious in origin (64%), followed by hematological (28%) and miscellaneous (8%) etiologies.\[10\]

Variations in the frequency of various diagnostic entities causing pancytopenia have been attributed to difference in methodology and stringency of diagnostic criteria,
geographic area, period of observation, genetic differences and varying exposure to myelotoxic agents, etc.[4]

The commonest cause of pancytopenia, reported in various studies throughout the world has been aplastic anemia.[4]

The incidence of megaloblastic anemia was 74.04% in our study. Incidence of 72% was reported by Khunger JM et al.; and 68%, by Tilak V et al.[5,6] All the above studies have been done in India, and they stress the importance of megaloblastic anemia being the major cause of pancytopenia. This is a rapidly correctable disorder and should be promptly notified.[6] Although bone marrow aspiration studies are uncommon in suspected cases of megaloblastic anemia, if the diagnosis does not appear straightforward or if the patient requires urgent treatment and hematological assays are not available, bone marrow aspiration is indicated. As facilities for estimating folic acid and vitamin B12 levels are not routinely available in most centers in India, the exact deficiency is usually not identified.[5]

Table 4: Age, sex distribution compared to those in other studies of pancytopenia

| S. no. | Authors                        | No. of cases | Age range (y) | M : F |
|--------|--------------------------------|--------------|---------------|-------|
| 1      | Khunger JM et al.[2] (2002)    | 200          | 2-70          | 1:2:1 |
| 2      | Kumar R et al.[1] (2001)      | 186          | 12-73         | 2:1:1 |
| 3      | Khodke K et al.[1] (2001)     | 50           | 3-69          | 1:3:1 |
| 4      | Tilak V et al.[1] (1999)      | 77           | 5-70          | 1:14:1|
| 5      | Present study                 | 304          | 2-80          | 1:2:1 |

Table 5: Physical findings compared to those in other studies

| Diseases                        | Physical findings | Splenomegaly | Hepatomegaly | Lymphadenopathy |
|---------------------------------|-------------------|--------------|--------------|-----------------|
|                                 |                   | A | B | C | A | B | C | A | B | C |
| Megaloblastic anemia            |                   | 40| 22| 42| 23| 23| 1 | 1 | 3 | - |
| Aplastic anemia                 |                   | - | 4 | 1 | 3 | - | - | 1 | - |
| Subleukemic leukemia            |                   | 8 | 4 | 10| 4 | 6 | - | - | - |
| MDS                             |                   | 4 | - | 4 | - | - | - | - | - |
| Hypersplenism                   |                   | 6 | - | 4 | - | - | - | - | - |
| Malaria                         |                   | 2 | 2 | 2 | - | - | 2 | - | - |
| Multiple myeloma                |                   | 1 | 1 | - | 1 | - | 1 | - | - |
| Disseminated tuberculosis       |                   | 1 | - | 1 | 1 | - | 1 | - | - |
| Storage disease                 |                   | - | 1 | - | 1 | - | - | - | - |
| CLL/ SLL                        |                   | 2 | 2 | 2 | 1 | - | 2 | 1 | - |

Table 6: Comparison of hematological parameters between major subgroups of cytopenias

| Parameters                      | aplastic anemia   | Megaloblastic anemia |
|---------------------------------|-------------------|----------------------|
|                                 | A     | B     | A     | B     |
| Hb (g/dL)                       | 1.3-8 | 2.8-6 | 2.4-7 | 1.8-9.2 |
| TLC x 10³ /µL                   | 0.2-3.0| 1.0-3.8| 0.7-3.6| 0.5-3.9 |
| Platelets (µL)                  | 8,000-| 10,000-| 10,000-| 12,000-|
|                                | 86,000-| 92,000-| 1,30,000| 95,000 |

Table 7: Comparison of peripheral blood findings with those in other studies

| Diseases                        | Total no. of cases | Anisopoikilocytosis | Nucleated RBC | Hypersegmented neutrophils | Immature WBC | Relative lymphocytosis | Reticulocytosis |
|---------------------------------|--------------------|---------------------|---------------|---------------------------|--------------|------------------------|----------------|
|                                 | 1 2 3              | 1 2 3               | 1 2 3         | 1 2 3                     | 1 2 3        | 1 2 3                  | 1 2 3          |
| Megaloblastic anemia            | 77 144 53          | 68 140 53           | 18 13         | 5 45                      | 20 18 1      | 6 14 7                 | 5 3 5           |
| Aplastic/Hypoplastic anemia     | 19 28 6            | 17 2 2              | -             | -                         | -            | -                      | -               |
| Hypersplenism                   | - 6                | - 5                 | -             | -                         | -            | -                      | -               |
| MDS                             | - 4                | - 2                 | -             | -                         | -            | -                      | -               |
| Subleukemic leukemia            | 4 10 1             | 1 1 1               | 4 1           | 2 10 1                    | -            | -                      | -               |
| Malaria                         | 2 - 3              | 2 - 1               | -             | -                         | -            | -                      | -               |
| Multiple myeloma                | 1 2 1              | 1 1 1               | -             | -                         | -            | -                      | -               |
| Disseminated tuberculosis       | - 1                | - 1                 | -             | -                         | -            | -                      | -               |
| Storage disease                 | 1 - 2              | 1 - 2               | -             | -                         | -            | -                      | -               |
| CLL/SLL                         | - 2 2              | - 2 2               | -             | -                         | -            | -                      | -               |

CLL/SLL: Chronic lymphocytic leukemia/Small lymphocytic lymphoma; MDS: Myelodysplastic syndrome
Table 8: Various causes of pancytopenia compared to those in other studies

| Causes                        | Khunger JM et al.[6] (2002) | Kumar et al.[5] (2003) | Khodke et al.[7] (2001) | Tilak V et al.[7] (1999) | Present study |
|-------------------------------|-----------------------------|------------------------|-------------------------|--------------------------|---------------|
| Aplastic anemia               | 28                          | 49                     | 7                       | 6                        | 19            |
| Megaloblastic anemia          | 144                         | 37                     | 22                      | 53                       | 77            |
| Hypersplenism                 | 4                           | 19                     | -                       | -                        | -             |
| Subleukemic leukemia          | 10                          | 20                     | 1                       | 3                        | 4             |
| Lymphoma                     | 2                           | 10                     | -                       | 2                        | -             |
| MDS                           | 4                           | 6                      | 1                       | -                        | -             |
| Marrow metastasis            | -                           | -                      | -                       | -                        | -             |
| Myelofibrosis                 | 2                           | 2                      | -                       | 2                        | -             |
| Malaria                       | 2                           | 5                      | -                       | 3                        | 2             |
| Enteric fever                 | -                           | -                      | -                       | -                        | -             |
| Malignant histiocytosis       | -                           | 1                      | -                       | -                        | -             |
| Disseminated TB               | 1                           | 1                      | 1                       | 1                        | -             |
| Multiple myeloma              | 2                           | -                      | 2                       | 1                        | 1             |
| Waldenstrom's macroglobulinemia | 1                       | -                      | 1                       | -                        | -             |
| AIDS                          | -                           | -                      | -                       | -                        | -             |
| Storage disorder              | -                           | -                      | -                       | -                        | 1             |

Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency to bleed. The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding the disease process; to diagnose, or to rule out the causes of, cytopenia; and in planning further investigations and management of cytopenic patients. Severe pancytopenia has significant relation with the clinical outcome and can be used as a prognostic indicator.

CONCLUSION

Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency to bleed. The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding the disease process; to diagnose, or to rule out the causes of, cytopenia; and in planning further investigations and management of cytopenic patients. Severe pancytopenia has significant relation with the clinical outcome and can be used as a prognostic indicator.

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