Original Research Article

A clinico-hematological study of pancytopenia in a tertiary care center

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Received: 11-11-2021 / Revised: 21-12-2021 / Accepted: 04-01-2022

Abstract

Background: Pancytopenia is triad of findings characterized by reduction in all three major formed elements of the blood: erythrocyte, leukocytes and platelets. The present study has been undertaken to study the clinical profile of the patient's presenting with pancytopenia, identify the underlying etiology leading to pancytopenia and bone marrow morphology due to various causes of pancytopenia. **Materials and Method**: An observational study was conducted on 100 patients of pancytopenia admitted in general medicine department. Selected patients were subjected for detailed clinical history, physical examination followed by lab investigations. Collected data were presented in tabulated or graphical form and were analyzed. **Result**: A total of 100 patients in the age range of 15- 85 years were taken in the study. There was male predominance with a male: female ratio of 2.2:1. Commonest clinical presentations were generalized weakness in 61% followed by fever in 47%. Most common physical findings were pallor observed in all patients followed by splenomegaly and hepatomegaly in 15 and 8 patients respectively. Bone marrow aspiration cytology showed hypercellular marrow in 62%, normocellular in 13% and hypocellular in 25%. Megaloblastic erthyopoeisis with hypercellular marrow were observed in 39 cases. 13 cases were diagnosed as acute leukemia and 02 cases were diagnosed as MDS. Hypocellular marrow was diagnosed in 25 cases out of which 18 cases were idiopathic aplastic anemia, 02 each of scrub typhus and SLE, 01 case each of post-partum aplastic anemia, disseminated tuberculosis and methotrexate induced. Normocellular marrow were observed in 04 cases of dimorphic anemia, 02 cases of Kala- azar, 01cases each of disseminated TB , falciparum malaria, metastatic adenocarcinoma and NHL. **Conclusion**: The present study concluded that Megaloblastic anemia is the most common and reversible cause of pancytopenia.

Keywords: Pancytopenia, megaloblastic anemia, bone marrow.

Introduction

Pancytopenia is triad of findings characterized by reduction in all three major formed elements of the blood: erythrocyte, leukocytes and platelets. Pancytopenia exist in an adult when the hemoglobin level is less than 13.5 gm/dl in males, or 11.5 gm/dl in females; the leukocyte count is less than 4×10^9/L and the platelet count is less than 150×10^9/ L[1]. It could be because of both hematopoietic and non-hematopoietic causes [2]. It is commonly insidious in onset but may pose diagnostic dilemma in new onset cases or when detected as an incidental finding. Pancytopenia is not a disease entity itself but mere manifestation of underlying pathology often characterized by signs and symptoms of anaemia and thrombocytopenia [3]. The underlying pathology leading to pancytopenia can be categorized into central type where bone marrow can be suppressed by variable causes such as destruction of marrow tissue by toxins, replacement by abnormal or malignant tissue, or suppression of normal marrow growth and differentiation. Second is peripheral type where increased peripheral destruction of cells occurs [4]. Possible mechanism includes rapid removal of defective cells from circulation, sequestration or destruction of cells by the action of antibodies and trapping of normal cells in a hypertrophied and overactive reticuloendothelial system [5]. The essential workup required to make a diagnosis of pancytopenia are often extensive which include detailed clinical history, medication history, physical examination and routine hematology including complete CBC, reticulocyte count, comment on peripheral smear and bone marrow examination [6]. Bone marrow examination is an invaluable diagnostic tool in practice of medicine and can expose the underlying pathology in about 75% pancytopenia cases [1,7]. In few selected cases additional testing and evaluations are required to establish a conclusive diagnosis. Despite doing extensive work up still there is a subset of patients who have unexplained cytopenia and are classified under the heading of idiopathic cytopenias of unknown significance [8]. The present study has been undertaken to study the clinical profile of the patient's presenting with pancytopenia, identify the underlying etiology leading to pancytopenia and bone marrow morphology due to various causes of pancytopenia.

Materials and Method

An observational study was conducted on patients of pancytopenia admitted in general medicine department of IGIMS, Patna, Bihar. The study was passed from the ethical committee of the institute. 100 consecutive patients were selected as per inclusion and exclusion criteria. Consent was taken from the patients. All new patients who

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were above 14 years of age, presented with peripheral pancytopenia (Hb<10gm/dl; TLC <4000/µL and Platelet <1,50,000/µL) and willing for bone marrow aspiration study as a part of diagnostic evaluation were included in the study. Those pancytopenic patients where bone marrow was not done/not required/ not consented were excluded from study. Those patients presented with pancytopenia but already diagnosed to have hematological disorder/ malignancy/HIV or on treatment with chemotherapy and other immunosuppressive agents were also excluded from study. Selected patients were subjected for detailed clinical history, physical examination followed by lab investigations which included complete hemogram, Erythrocyte sedimentation rate (ESR), Peripheral blood smear study and Reticulocyte count. Bone marrow was performed in all patients and biopsy in selected patients only. Viral studies (HBS Ag, Anti-HCV and HIV), LFT, KFT, CXR, and USG Abdomen were done in all cases. In selected cases viral study for hepatitis A, Epstein-Barr virus and cytomegalovirus as well as estimation for Vitamin B12, folate level, Coomb's test, ANA and anti-dsDNA was done. Data collected after history, clinical examination and investigation were presented in tabulated or graphical form and were analyzed.

Result

A total of 100 patients in the age range of 15- 85 years were taken in the study. There was male predominance with a male (69): female (31) ratio of 2.2:1. Commonest clinical presentations were generalized weakness in 61% followed by fever in 47%. Most common physical findings were pallor observed in all patients followed by splenomegaly and hepatomegaly in 15 and 8 patients respectively. Hemoglobin (Hb) varied from 1.9gm/dl to 12.5gm/dl; the lowest Hb was recorded in 40 years old female who was later diagnosed as a case of systemic lupus erythematosus (SLE). Similarly, TLC ranged between 1800 /cumm to 3700 /cumm and platelet count 10,000 to 90,000 /cumm. Bone marrow aspiration cytology showed hypercellular marrow in 62%, normocellular in 13% and hypocellular in 25%. There was spectrum of disease which can lead to pancytopenia with hyperplastic bone marrow. Out of which megaloblastic erythropoiesis with hypercellular marrow were observed in 39 cases. Rest of the cases with hypercellular marrow and peripheral pancytopenia showed hypersplenism in 06 cases and dimorphic anemia in 02 patients. In hematological malignancy, 13 cases of acute leukemia with highest incidence in age range of 15-24 (08), 02 each in age range of 25-34 and 35-44 and 01 case in 45-54 age groups. 02 cases were diagnosed as MDS and were advised for karyotyping. The maximum clustering of hypoplastic marrow were in the age range of 15-24 (10 cases) followed by 5 cases in the age range of 45-54. Out of 25 cases of hypocellular marrow, 18 were diagnosed as idiopathic aplastic anemia and 02 each of scrub typhus and SLE. 01 case of post-partum aplastic anemia was reported in young female. 01 case of hypocellular marrow was encountered in patient suffering from disseminated tuberculosis. 01 case showed panctopenia after taking methotrexate for rheumatoid arthritis. Normocellular marrow were observed in 04 cases of dimorphic anemia, 02 cases of Kala-azar, 01 cases each of disseminated TB and falciparum malaria and 01case each of metastatic adenocarcinoma and NHL. In 03 cases, bone marrow aspiration cytology was reported as normocellular marrow with reactive change. No etiology could be established even after extensive workup.

Table 1: Signs and symptoms of the patients

S. No.	Signs & Symptoms	No. of patients'	Percentage
1	Weakness	62	62%
2	Fever	47	47%
3	Vomiting	13	13%
4	Palpitation	05	5%
5	Bodyache	05	5%
6	Giddiness	05	5%
7	Loss of appetite	07	7%
8	Dyspnea	04	4%
9	Chest pain	01	1%
10	Hemoptysis	02	2%
11	Recurrent nasal bleed	03	3%
12	PV bleeding	01	1%
13	Melena	02	2%
14	Epigastric pain	04	4%
15	Loose motion	04	4%
16	Oral ulcers/glossitis	02	2%
17	Facial swelling	01	1%
18	Hepatomegaly	08	8%
19	Splenomegaly	15	15%
20	Lymph node	02	2%
21	Jaundice	03	3%

Table-2: Various causes of pancytopenia

Diagnosis	Cellularity	Male	Female	Total
Megaloblastic anemia	Hypercellular	27	12	39
Acute leukemia	Hypercellular	09	04	13
Hypersplenism	Hypercellular	05	01	06
Dimorphic anemia	Hypercellular	-	02	02
Myelodysplastic syndrome	Hypercellular	02	-	02
Non Hodgkins Lymphoma	Normocellular	01	-	01
Dimorphic anemia	Normocellular	02	02	04
Disseminated tuberculosis	Normocellular	01	-	01
Falciparum malaria	Normocellular	01	-	01
Leishmaniasis	Normocellular	02	-	02
Metastatic	Normocellular	-	01	01

Idiopathic aplastic anemia	Hypocellular	14	04	18
Scrub typhus	Hypocellular	02	-	02
SLE	Hypocellular	-	02	02
Drug induced	Hypocellular	-	01	01
Post-partum aplastic anemia	Hypocellular	-	01	01
Disseminated tuberculosis	Hypocellular	01	-	01
Undiagnosed	Normocellular	02	01	03

Discussion

In clinical practice pancytopenia is somewhat a common problem with extensive differential diagnosis. A great variation in the frequency of various etiological entities leading to pancytopenia has been documented by different study group worldwide. This is possibly attributable to the geographic area, demographic profile of patient under study, nutritional status, prevalence of infective pathology, exposure to chemicals, toxins and many more undocumented factors [7,9].

In our study, patients in the age range of 15-85 years were evaluated. We also observed male preponderance like other similar studies [10,11]. The most frequent affected age group among male was 15-24 with 28% cases. Amongst female maximum clustering were seen in 25-34 years with 11 cases. The most common clinical presentation was generalized weakness in 61% cases followed by fever in 47%. Bleeding manifestation from various sites were 8%. Pallor was the most common physical sign observed in 100% of cases. Splenomegaly was present in 15% and hepatomegaly in 08%. B N Gayathri et al.[12], Rangaswamy M et al.[13] and Chandra K et al[14] also observed fever and generalized weakness as common symptoms and pallor as the commonest sign. Khodke K. et al.[15] observed fever as the commonest presentation in only 40% cases followed by weakness in 30% cases and bleeding manifestation in 20%. Similarly, Chandra K et.al[14] also found bleeding manifestation in 24.4% cases which is significantly higher than present study. Even splenomegaly and hepatomegaly was present in 33.7% and 22.8% cases respectively in their study. This difference supports the variation in frequency of etiologies causing pancytopenia in particular region.

The fact that B12 deficiency is the main causes of megaloblastic anemia in developing countries especially in Indian subcontinent are supported by several studies done by different authors in last 20 years from different geographical region of the country. The overall incidence of megaloblastic anemia noted in the various studies conducted in India so far vary from 22.3 to 72% followed by aplastic anemia which showed an incidence of 10%-52.7% in all pancytopenic patients [16,17,18,19]. In present study also, the major cause of pancytopenia was diagnosed as megaloblastic anemia followed by hypolastic /aplastic anemia in the age range of 15-24 years with male predominance in both conditions. These etiological findings as the most frequent and second frequent were also observed by other researchers like B N Gayathri et al.[12], Khodke K et al.[15] and Khunger et al.[18]. This observation is in sharp contrast with industrialized and developed countries of western world where leukemia is the leading cause of pancytopenia compared to vitamin deficiency and infective pathology of developing countries [1,4]. In present study, 13% cases of acute leukemia were documented constituting third frequent cause of pancytopenia similar to Kumar R. et al who reported 12.4 % of overall incidence of acute leukemia [10]. All these patients of acute leukemia were later subjected to flow cytometry for typing and referred to our state cancer institute for further management.

Incidence of aplastic anemia is more in Asian countries as compared to west including Indian subcontinent probably due to lower socio-economic status, high exposure to pesticides due to maximum dependency on agriculture, chemicals, toxins and pathogens [20,21,22]. Present study observed male predominance of hypocellular marrow where no cause could be established and were further categorized into idiopathic aplastic anemia. Studies in Philippines [17] and Nepal [23] also found high incidence of aplastic anemia among males compared to females. On the contrary, study from Pakistan by Das Makheja K et al[2] found equal incidence of aplastic anemia among male and females. In contrast to other studies, we encountered 02 cases of scrub typhus presented with fever, bodyache, joint pain, pancytopenia and hypocellular marrow. They were treated by appropriate antibiotics with full clinical and hematological recovery. Two female patients each in the age range of 15-24 and 35-44 presented with fever, bodyache, rashes and new onset pancytopenia with hypocellular marrow. On further evaluation they were diagnosed as SLE and managed accordingly. Generally, patients suffering from SLE presents with cellular marrow but hypocellularity can be found which suggest disease activity [17]. One female was referred to hematological center as she was diagnosed post-partum aplastic anemia. We encountered one case that presented with fever and cough and was on irregular treatment for tuberculosis. Further evaluation revealed pancytopnia with hypoplastic marrow which is not a common observation for disseminated tuberculosis. Jain A et al also found pancytopenia in disseminated tuberculosis and they proposed that it should always be kept as differentials in our country. In TB, degree of pancytopenia is influenced by the duration of disease not by the severity [3]. One patient of rheumatoid arthritis on methotrexate presenting with weakness, oral ulcer and bleeding symptom diagnosed as drug induced pancytopnia.

We encountered 13% cases with normocellular marrow. Rangaswamy M et. al. found normocellular marrow in 11% of cases. Out of 13, in 03 cases definite etiology could not be established and rest of the cases presented with variable underlying pathology. A 60-year-old female presented with generalized weakness, low grade fever and pancytopenia for 3-4 months. Meticulous evaluation including bone marrow aspiration showed metastasis. Similarly, one male patient presented with pancytopenia later diagnosed as Non-Hodgkin's Lymphoma. One patient each of disseminated TB and falciparum malaria showed normocellular marrow. Though Bihar is endemic for Kala-azar, we come across only those cases that show some atypical presentation. We found 02 cases during our study period that were positive for rK39 antigen test as well as showed LD in bone marrow. 04 cases of dimorphic anemia showed normoblastic erythropoiesis with micronormoblast.

In present study, we encountered variable causes leading to pancytopenia. But above all the prevalence of nutritional anemia particularly megaloblastic anemia remained the leading cause of pancytopenia under evaluation. The second position is being occupied by aplastic anemia followed by cases of acute leukemia. This observation is quite helpful for primary care physicians who are the first contact doctor for the general population in initiating the treatment / referral without much delay which may be helpful in avoiding further complication. But at the same time they should be aware of the different causes and morphological features of pancytopenia present in their region. Recent reports have also observed certain rare causes of pancytopenia that include breast carcinoma, myxedema coma, or Stevens-Johnson syndrome [24, 25, 26]. We also observed few infrequent cases of pancytopenia like SLE and Scrub typhus. Though these causes are not rare but not commonly documented in previous studies. So timely referral to higher centers where meticulous workup may help to achieve precise diagnosis of pancytopenia will help in timely interventions and will improve the survival outcome [27].

Conclusion

Pancytopenia is a clinical entity associated with numerous reversible or irreversible etiologies. Megaloblastic anemia is the most common and reversible cause of pancytopenia. This study emphasizes on the knowledge of varied etiologies leading to pancytopenia in reference to loco regional background which will help to narrow down the differentials and hasten the focused management.

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Conflict of Interest: Nil Source of support: Nil