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A STUDY OF CLINICOHEMATOLOGICAL PROFILE AND BONE MARROW FINDINGS IN BICYTOPENIA AND PANCYTOPENIA

Hematology

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ABSTRACT

Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e., red cells, white cells or platelets. Bicytopenia is reduction in any of the two cell lines and pancytopenia is reduction in all the three. There is a considerable overlap between the causes and diagnostic approach of bicytopenia and pancytopenia. The etiology of pancytopenia and bicytopenia varies in different populations depending on nutritional status, cultural background, climate, season and prevalence of infections in the society. It often creates a diagnostic challenge to physicians and the knowledge of accurate causes of this condition is crucial in the management of the patient. Thus, a systematic approach is necessary to narrow down the differential diagnosis. The main aim of this study is to determine the common causes of bicytopenia and pancytopenia in our tertiary care centre in different sexes and age groups and to evaluate clinico-haematological profile and bone marrow findings in patients with bicytopenia and pancytopenia. Out of the total 41 cases, 25 were of pancytopenia and 16 were of bicytopenia. The most common cause of bicytopenia/ pancytopenia was megaloblastic anaemia followed by dimorphic anaemia followed by acute leukemia and aplastic anaemia. Some rare causes were also found. So through this study, we would like to emphasize that as the aetiology of large proportion of pancytopenia cases is reversible so an early, accurate and prompt intervention can be lifesaving.

KEYWORDS

Pancytopenia, Bicytopenia, Megaloblastic Anemia

INTRODUCTION

Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e., red cells, white cells or platelets. Bicytopenia is reduction in any of the two cell lines and pancytopenia is reduction in all the three cell lines[1].

There is a considerable overlap between the causes and diagnostic approach of bicytopenia and pancytopenia. Thus, pancytopenia is not a disease entity, but a triad of findings, resulting from various disease processes.

Patients of bicytopenia/ pancytopenia usually present with fever, fatigue, dizziness, weight loss, anorexia and night sweats. The common clinical signs are pallor, bleeding, splenomegaly, hepatomegaly, and lymphadenopathy[2].

The underlying mechanisms maybe secondary to decreased marrow production, marrow infiltration, bone marrow suppression, ineffective hematopoiesis or increased peripheral destruction[3].

There are many studies highlighting pancytopenia in different study groups. In those studies, commonest causes for pancytopenia were hypersplenism[4], aplastic anaemia[18] and megaloblastic anaemia[5].

A systematic approach is necessary to reach to the diagnosis. This involves a proper history taking and physical examination. Patients having laboratory values suggestive of pancytopenia/bicytopenia further require sequential examination of reticulocyte count, peripheral blood smear examination, bone marrow aspiration and/or biopsy.

As there are various differential diagnosis for bicytopenia/ pancytopenia, it often a creates diagnostic challenge to physicians and the knowledge of accurate causes of this condition is crucial in the management of the patient.[6]

AIMS AND OBJECTIVES

1. To determine the common causes of Bicytopenia and Pancytopenia in our tertiary care center in different sexes and age groups.
2. To evaluate clinico-haematological profile and bone marrow findings in patients with Bicytopenia and Pancytopenia.

MATERIAL & METHODS

This study was conducted at our tertiary care centre from January 2021 to June 2022. The study included patients 41 patients of Bicytopenia or Pancytopenia on routine hematological investigations and registered as OPD/ IPD patients.

Clinical details and history were recorded. A detailed clinical examination and a complete hematological workup was done. Patients showing all three or any two of the inclusion criteria on complete blood examination were included in this study.

A) Inclusion criteria – [7]

Presence of all 3 or any 2 of the following in patients >12yrs of age:

1) Hemoglobin <10g/dl
2) Total leukocyte count (TLC) <4000/dl
3) Platelet count <1,00,000/ dl

B) Exclusion Criteria

1) Diagnosed cases of malignancy on chemotherapy and radiation were excluded.
2) Children below age 12 years were excluded.

Patients who fulfilled the above-mentioned criteria were subjected to bone marrow examination with due informed written consent. Bone marrow aspiration was obtained in all the cases, of which material was inadequate to opine in 6 cases. In such cases bone marrow biopsy aided in the diagnosis.

OBSERVATIONS AND RESULTS

Out of the total 41 cases, 25 were of pancytopenia and 16 were of bicytopenia. There was a slight preponderance among males. Male to female ratio was approximately 1.41:1.

The age of the patients varied between 13 to 75 years with maximum cases between 21-40 years.

Patients presented with a wide variety of symptoms among which generalised weakness was the most common (58.54%) followed by fever (34.15%) and breathlessness (26.83%).

In the past history, 11 patients (26.9%) had received previous blood transfusions and 5 (12.2%) patients had a history of chronic alcohol intake.

On physical examination, the commonest sign was pallor, seen in all the patients (100%). Splenomegaly and hepatomegaly were noted in 12 patients (29.27%) and 8 patients (19.5%) respectively.

Lymphadenopathy was noted in 7 patients (17.07%), out of which 4 patients (9.76%) had generalised lymphadenopathy and 3 patients (7.32%) had cervical lymphadenopathy.

The range of haemoglobin, Total leukocyte count and platelet count were studied.

Haemoglobin value was found to be ≤10g/dl in all the patients. Most of the patients (n=22) had haemoglobin percentages between the range 5.1-8.0 g%. Most of the patients (n=22) had total leucocyte count >2500/mm^3. Leukopenia (TLC <4000/mm^3) was seen in 33 patients (80.49%) while leucocytosis (TLC >11,000/mm^3) was seen in 4 patients (9.76%). Most of the patients (n=27) had platelet count <50,000 /mm3.

Peripheral blood smear findings-

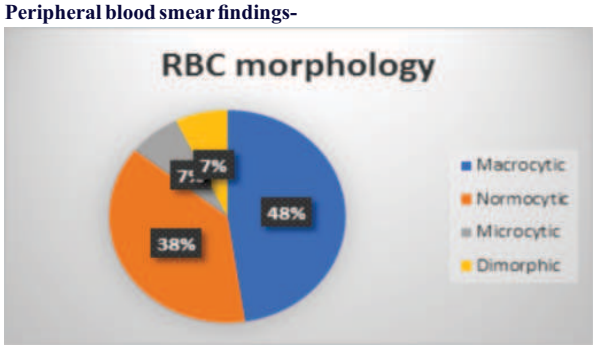


Figure 1. RBC morphology

Anisopoikilocytosis was seen in 15 patients (36.58%) while 7 patients (17.07%) showed anisocytosis. The predominant RBC morphology was macrocytic, seen in 20 patients (48.78%) while normocytic picture was noted in 15 patients (36.58%) and 3 patients (7.32%) showed microcytic picture. Dimorphic picture was observed in 3 patients (7.32%).

The other important morphological variations were macroovalocytes in 8 patients (19.51%), basophilic stippling in 7 patients (17.07%) and cabot rings in 6 patients (14.63%).

Hypersegmented neutrophils were noted in 12 patients (29.27%). Circulating blasts were seen in 3 cases (case of blast transformation in a known case of myelofibrosis, one case of acute promyelocytic leukemia and other case of Acute lymphoblastic leukemia).

Bone marrow studies

Table No 1: Causes (Etiology) of bicytopenia/pancytopenia

Causes (Etiology) of bicytopenia/pancytopenia	Number	%
Megaloblastic anaemia	24	58.53
Dimorphic anaemia	5	12.2
Acute leukemia	3	7.32
Aplastic anaemia	3	7.32
Hemolytic anaemia	1	2.44
Blast transformation in a known case of myelofibrosis	1	2.44
Plasma cell myeloma	1	2.44
Bone Marrow involvement by NHL	1	2.44
Hemophagocytic syndrome	1	2.44
Bone marrow metastasis	1	2.44

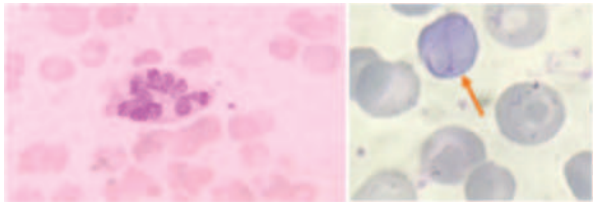
On bone marrow examination, the most common cause of bicytopenia/ pancytopenia was megaloblastic anaemia which was found in 24 patients (58.53%) followed by dimorphic anaemia found in 5 patients (12.2%).

Bone marrow in the present study showed three different types of cellularity- hypercellular, normocellular and hypocellular.

Table No.2: Bone marrow cellularity in cases of bicytopenia/ pancytopenia

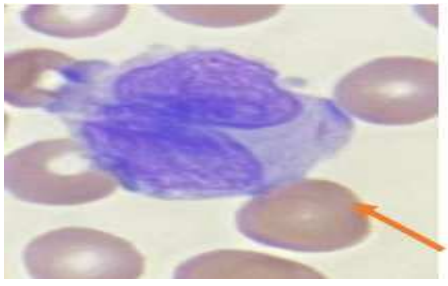
Bone marrow findings-Cellularity	Number	%
Hypocellular	4	9.76
Hypercellular	34	83
Normocellular	3	7.32

Peripheral smears



Microphotograph.1 **Microphotograph.2**

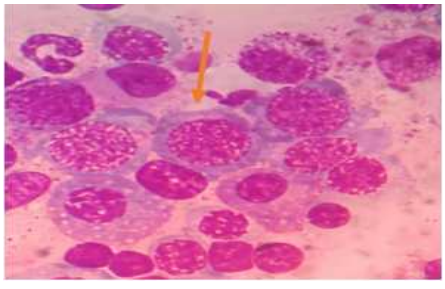
Peripheral smear showing hypersegmented neutrophil and cabot rings in a case of megaloblastic anemia (1000X, Leishman stain)



Microphotograph.3 (1000X-Leishman stain)

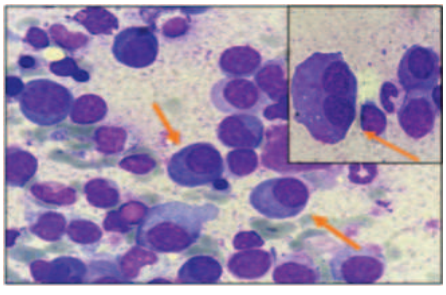
Peripheral smear in a case of acute promyelocytic leukemia showing myeloblasts with Auer rods (arrow)

Bone Marrow aspirate-



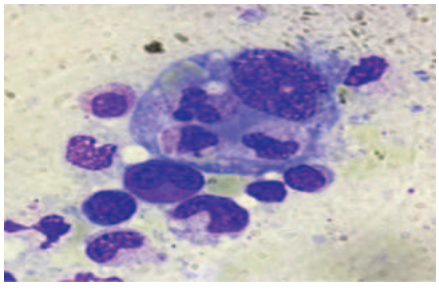
Microphotograph 4. (1000X- Leishman stain)

Bone marrow aspirate in a case of megaloblastic anaemia showing sieve like chromatin in megaloblasts (arrow)



Microphotograph 5. (400X- Leishman stain)

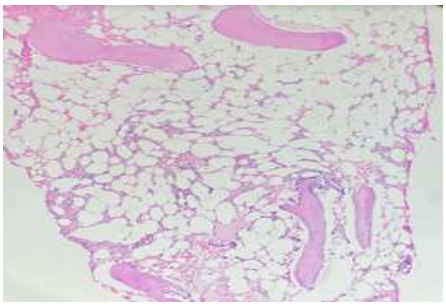
Bone marrow aspirate in case of plasma cell myeloma. Inset showing atypical plasma cells



Microphotograph 6. (1000X- Leishman stain)

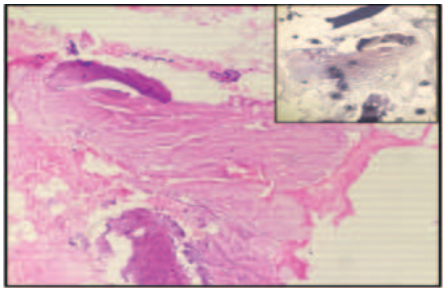
Bone marrow aspirate in a case of hemophagocytic syndrome

Bone marrow biopsy



Microphotograph 7. (100X, H&E stain)

Bone marrow biopsy in a case of aplastic anemia showing hypocellular marrow



Microphotograph 8. (100x- H & E stain)

Bone marrow biopsy in a known case of myelofibrosis showing hypocellular marrow with increased fibrosis. Inset showing Reticulin grade III

DISCUSSION

In this study of 41 patients, the age of the patients ranged from 13 to 75 yrs. Patients most commonly belonged to the age group of 21-40 yrs, which was similar to Pooja Agarwal, et al., Sweta, et al., Vishal Narote, et al studies.[8,9,10] While Sridevi Hanaganahalli Basavaiah, et al. & Jain and Naniwadekar, et al. studies noted maximum cases in 4th decade.[11,4] In the present study, male to female ratio of 1.41:1 was obtained with a slight male preponderance. In contrast to the other studies, a study conducted by Vishal Narote, et al. showed a slight female preponderance in their studies.[10]

Clinical presentations in pancytopenia can be attributed to anaemia, leucopenia, and/or thrombocytopenia. Generalised weakness was the most common presenting complaint and was observed in 58.54% patients followed by fever (34.15%) and breathlessness (26.83%). Similar findings were seen in studies by Sridevi Hanaganahalli Basavaiah, Gayathri and Rao, et al. and Pooja Agarwal, et al. studies also[11,5,8]

On Examination-

Pallor was the most common sign on clinical examination in various studies [8-16]. This was in concordance with our study in which pallor was seen in all the patients.

In the present study, splenomegaly was noted in 29.27% patients. While a much higher incidence of splenomegaly was noted in Sridevi Hanaganahalli Basavaiah, et al. study (66.75%).[11] A slightly higher incidence of splenomegaly in Pooja Agarwal, et al. study, could be attributed to 6 cases of chronic myeloproliferative neoplasm.[8]

Hepatomegaly was found in 19.5% patients in our study. A much higher incidence of hepatomegaly was seen in Sridevi Hanaganahalli Basavaiah, et al. and Vishal Narote, et al. studies which accounted for 50% and 33.96% cases respectively.[11,10]

Lymphadenopathy was noted in 17.07% cases in our study which was similar to Vishal Narote, et al. and Sandeep Ojha, et al. in which lymphadenopathy was seen in 22.64% and 17.3% patients respectively.[10,12]

On peripheral blood smear examination, in the present study, predominant picture was macrocytic (48.78%) which was in concordance with Pooja Agarwal et al. (45%) and Sweta at el. (49%) studies.[8,9] This could be because megaloblastic anaemia was reported as the commonest cause of bicytopenia/ pancytopenia in these studies. In a study by Gayathri et al., predominant blood picture was dimorphic (37.5%) followed by macrocytic (31.7%).[5] Microcytic picture was seen in 7.32% patients in our study. This was similar to Pooja Agarwal et al.study in which microcytic picture was found in 10% patients.[8]

Hypersegmented neutrophils were seen in 12 patients (29.27%) in this study. A much higher percentage of hypersegmented neutrophils (51.35%) was seen in Graham, et al. [13] whereas in a study by Khunger, et al.[14], an absence of hypersegmented neutrophils was noted.

Table 3. Comparison between common causes of Pancytopenia/ Bicytopenia in various studies

Sr. No	Study	Commonest cause	2nd common	3rd common	4th common
1	Jyoti SK, et al. [15] (n=166)	Hypersplenism (33.17%)	Aplastic anaemia (13.9%)	Infection induced pancytopenia (10.8%)	Pancytopenia with normal active marrow (9.6%)
2	Pooja Agarwal et al. [8]	Megaloblastic anaemia (37.5%)	Erythroid hyperplasia (20%)	Aplastic anaemia (10%)	Chronic Myeloid Leukemia (7.5%)
3	Gayathri and Rao, et al[5]	Megaloblastic anaemia (74.04%)	Aplastic Anaemia (18.26%)	Subleukemic leukemia (3.85%)	Malaria (1.93%)
4	Vishal Narote et al. [10] (n=53)	Megaloblastic anaemia (52.8%)	Acute leukemia (AML) (20.8%)	Normoblastic erythroid hyperplasia (11.32%)	Aplastic anaemia (9.4%)
5	Jain and Naniwadekar [4]	Hypersplenism (29.2%)	Infections (25.6%)	Myelosuppressants (16.8%)	Megaloblastic anaemia (13.2%)
6	Sandeep Ojha et al. [12]	Megaloblastic anaemia (25.6%)	Acute leukemia (16%)	Hypoplastic marrow (14%)	Metastasis (8.9%)
7	Sweta, et al. [9] (n=100)	Megaloblastic Anaemia (66%)	Aplastic anaemia (18%)	Malaria (6%)	Kala azar (4%)
8	Sridevi Hanaganahalli Basavaiah et al. [11]	Infections (43.8%)	Megaloblastic anaemia (23.25%)	Chronic liver disease (14.25%)	Neoplastic condition (12.5%)
9	Reddy GP et al.[16]	Megaloblastic anaemia (38.1%)	Aplastic anaemia (26.2%)	Subacute leukemic leukaemia (9.5%)	Malaria (7.1%)
10	Present study	Megaloblastic anaemia (58.53%)	Dimorphic anaemia (12.2%)	Acute leukemia (7.32%)	Aplastic anaemia (7.32%)

The most common cause of bicytopenia and pancytopenia differed in various studies. The commonest cause of bicytopenia and pancytopenia in our study was megaloblastic anaemia (58.53%) followed by dimorphic anemia (12.2%), acute leukemia (7.32%) and aplastic anaemia (7.32%). This was in accordance with various studies.[8,5,10,12,9,16] This reflects the higher prevalence of nutritional deficiencies in Indians.

This was in contrast to Jyoti SK, et al.& Jain and Naniwadekar studies in which hypersplenism was the commonest aetiology accounting for 33.17% and 29.2% cases respectively. [15, 4] In Sridevi Hanaganahalli Basavaiah, et al. study, infections were found the be the commonest cause accounting for 43.8% cases.[11]

In our study, megaloblastic anaemia was found in 24 (58.53%) patients. Bone marrow was hypercellular and showed erythroid hyperplasia with megaloblastic maturation. In 5 patients (12.2%), history of chronic alcoholism was found. Other additional features, macrocytosis, macro-ovalocytes, hypersegmented polymorphs,

reduced serum cobalamin and red cell folate levels can serve as an aid in the diagnosis. [17]

However, due to financial constraints, serum cobalamine and folate levels were not done in our study. As megaloblastic anaemia is a rapidly correctable disorder, it should be rectified promptly. [13]

In the present study, dimorphic anaemia was the second most common cause(12.2%) of bicytopenia/ pancytopenia. Acute Leukemia was seen in 3 patients (7.32%) among which 2 were diagnosed with acute promyelocytic leukemia and 1 was diagnosed with acute lymphoblastic leukemia. In studies conducted by Vishal Narote et al. and Sandeep Ojha et al., leukemia was the second most common etiology accounting for 20.8% and 16% cases respectively. [10,12] In leukemia, there occurs a combination of suppression of normal hematopoeisis along with replacement of bone marrow by leukemic cells. Thus, leading to immunosupression and pancytopenia.

In the present study, aplastic anaemia was noted in 3 cases. Aplastic anaemia was the most common cause of pancytopenia in Santra, et al. [18] study, accounting for 22.72% cases. While aplastic anaemia was the second most common cause in Reddy GP, et al. (26.2%), Sweta, et al.(18%) and Jyoti SK, et al. (13.9%) studies.[16,9,15]

A single case of Blast transformation in a known case of myelofibrosis, showing 52% blasts, hypocellular bone marrow and reticulin grade III was reported in the present study.

Similar to our study, a single case of multiple myeloma was also reported in Tilak V et al.study.[19]

In the present study, one case of metastatic deposits in bone marrow was encountered. Patient was a known case of carcinoma breast for 2 months with liver metastasis. In a few studies, metastatic deposits have been reported as a cause of pancytopenia.[20] Sandeep Ojha et al. study also reported metastasis as the cause of bicytopenia/ pancytopenia in 8.9% cases.[12]

A single case of hemolytic anaemia was reported in the present study. Patient had pancytopenia, high reticulocyte count(5%), hyperbilirubinemia and mild erythroid hyperplasia on bone marrow examination. Flow cytometry for CD55 and CD 59 & enzyme study for G6PD were advised.

A solitary case of hemophagocytic syndrome was reported in the present study, with moderate increase in number of macrophages with evidence of hemophagocytosis, severe pancytopenia, splenomegaly and recent febrile illness. Hemophagocytic syndrome was reported as the cause of pancytopenia in 2 cases in Sandeep Ojha et al. study.[12] Of them one patient succumbed to the disease. Thus, emphasising the importance of early diagnosis and treatment as it has poor prognosis.

In the present study, bone marrow involvement by Non Hodgkins lymphoma was reported in a 70 year male patient. A study by Sridevi Hanaganahalli Basavaiah et al. reported a single case of Hodgkins lymphoma and 7 cases of Non Hodgkins lymphoma as the cause of pancytopenia.[11]

We didn't have any case of hypersplenism or infectious disease presenting as bicytopenia/ pancytopenia in our study.

In the present study, 83% patients had hypercellular marrow, of which 67.64% patients had megaloblastic anaemia. Other causes were dimorphic anaemia, nutritional anaemia, acute leukemia, plasma cell myeloma, metastatic marrow, bone marrow involvement by NHL. Similar to the present study, Vishal Narote et al. and Sweta et al studies also reported hypercellularity in 79.24% and 72% cases.[10,9]

Hypocellular marrow was seen in 9.76% (n=4) cases in the present study. Of which 3 cases were of aplastic anaemia and 1 case of blast transformation in a known case of myelofibrosis. In Reddy GP et al study, major proportion of cases (47.6%) showed hypocellular marrow with aplastic anaemia as the second most common cause.[16]

CONCLUSION

It is essential to be aware of the causes of bicytopenia /pancytopenia as it is a commonly encountered hematological condition and there are a wide range of causes which differ depending on the geographic areas and genetic differences. Thus, a systematic approach is necessary to narrow down the differential diagnosis.

As the aetiology of large proportion of pancytopenia cases is reversible so an early, accurate and prompt intervention can be lifesaving.

Megaloblastic anaemia was the most common cause in our study. We would like to emphasise that Vit B12 and folic acid should be incorporated in the diet to avoid the occurrence of megaloblastic anaemia. To combat this issue food fortification & Vitamin B12 and folic acid supplementation can be done.

REFERENCES

1. Bates I, Bain BJ. Approach to diagnosis and classification of blood diseases. In: Lewis SM, Bain BJ, Bates I, editors. Dacie and Lewis Practical Haematology. 10th ed. Philadelphia: Churchill Livingstone; 2006. p. 609-24. 2
2. Imbert M, Scoazec JY, Mary JY, Jouzult H, Rochant H, Sultan C. Adult patients presenting with pancytopenia: a reappraisal of underlying pathology and diagnostic procedures in 213 cases. Hematologic pathology. 1989 Jan 1;3(4):159-67.
3. Brodsky RA. Acquired Aplastic anemia. In: Greer JP, Arber DA, Glader B, List AF, Means RT, Paraskevas F, et al., editors. Wintrobe's clinical hematology. 13 th ed. Philadelphia. Lippincott William and Wilkins. 2014. p. 965-74..
4. Jain A, Naniwadekar M. An etiological reappraisal of pancytopenia-largest series reported to date from a single tertiary care teaching hospital. BMC Blood Disorders. 2013 Dec;13(1):1-9.
5. Gayathri BN, Kadam SR. Pancytopenia: a clinicohematological study. J Lab Physicians. 2011; 3: 15-20. https://bit.ly/2LiKQXL
6. Pathak R, Jha A, Sayami G. Evaluation of bone marrow in patients with pancytopenia. J Patho Nepal. 2012; 2: 265-271.
7. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia--a six year study. The Journal of the Association of Physicians of India. 2001 Nov 1;49:1078-81.
8. Agarwal P, Asbah Shams PP, Kumar H, Nigam A. Evaluation of pancytopenia in adults through haematological parameters and bone marrow studies. Indian Journal of Pathology and Oncology. 2018 Oct;5(4):548-53.
9. Barik S, Chandoke RK, Verma AK. A prospective clinico-hematological study in 100 cases of pancytopenia in capital city of India. Journal of applied hematology. 2014 Apr 1;5(2):45.
10. NAROTE DV, JHAM R. CLINICO HAEMATOLOGICAL STUDY IN CASES OF PANCYTOPENIA. ijmscrr [Internet]. 15Apr.2022 [cited 17Jan.2023];5(02):Page: 89-9. Available from: https://ijmscrr.in/index.php/ijmscrr/article/view/187
11. Basavaiah SH, Rai S, Suresh PK, Shivaprasad SM, Khandelia B. Clinicopathological Diversity of Pancytopenia: A Series of 400 Cases. Journal of Clinical & Diagnostic Research. 2018 Mar 1;12(3).
12. Ojha S, Haritwal A, Meenai FJ, Gupta S. Bone marrow examination findings in cases of pancytopenia-a study from central India. Indian Journal of Pathology and Oncology. 2016 Jul;3(3):479-84.
13. Graham S, Marla NJ, Fernandes H, Jayaprakash CS. A clinicohematological evaluation of pancytopenia in a tertiary care hospital in South India. Muller Journal of Medical Sciences and Research. 2015;6(1):5-9.
14. Khunger JM, Arulselvi S, Sharma U, Ranga S, Talib VH. Pancytopenia--a clinico haematological study of 200 cases. Indian journal of pathology & microbiology. 2002 Jul 1;45(3):375-9.
15. Jyoti SK, Badhe BA, Dutta TK, Sajjan J. Clinicopathological Study of Adult Pancytopenia with Special Reference to Bone Marrow Biopsy.
16. Reddy GP, Rao KV. Clinical features and risk factors of pancytopenia: a study in a tertiary care hospital. Int J Adv Med. 2016 Jan;3(1):68-72.
17. Kumar V, Khare M, Kishore M, Sharma M, Marwah S, Nigam AS, Singh P. Diagnostic approach of new-onset pancytopenia: study from a tertiary care center. Annals Pathol Lab Med. 2018 Aug;5:0.
18. Santra G, Das BK. A cross-sectional study of the clinical profile and aetiological spectrum of pancytopenia in a tertiary care centre. Singapore medical journal. 2010 Oct 1;51(10):806.
19. Tilak V, Jain R. Pancytopenia--a clinico-hematologic analysis of 77 cases. Indian journal of pathology & microbiology. 1999 Oct 1;42(4):399-404.
20. Pendkur G, Singhal P, Somasundaram V, Raghavendra SK, Sharma S. Clinicopathological study of new onset pancytopenia: An experience of largest study from a tertiary care center of western India. Medical Journal of Dr. DY Patil Vidyapeeth. 2021 May 1;14(3):283.