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Original Research Paper

Clinical Profile and Etiopathological Causes of Bicytopenia and Pancytopenia in A Tertiary Care Hospital in South India

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ABSTRACT:

Review and Background: Pancytopenia is a hematologic condition characterized by a decrease in all three peripheral blood lineages. Bicytopenia is the condition where there is a decrease in two of the hematopoietic lineages. Both pancytopenia and bicytopenia are usually a manifestation of one of a variety of diseases which may affect the bone marrow. Pancytopenia in particular, is a strong indicator for bone marrow examination. Effective treatment heavily depends on accurately diagnosing the etiology of the same. **Aim and Objectives**: 1) To generate data on the clinical profiles and etiological causes of pancytopenia and bicytopenia in South India. 2) Analyze the use of bone marrow examination in the diagnosis of hematological malignancies. **Methodology**: The data was retrieved from medical records and LIS system of the institution. We used the WHO approved criteria of anemia to classify cases into four categories; mild, moderate, severe and life threatening anemia. We further sub classified the data into bicytopenia and pancytopenia and analyzed the data for significant correlation. **Statistics**: The data retrieved was tabulated and represented in percentages, measures of central tendency and analyzed statistically for correlation between the severity of anemia and disease outcome using T - Test and ANOVA interpretation. The descriptive statistics for the tests were represented as graphs and charts. **Results**: During the period of January 2020 to December 2022, we encountered 414 cases of cytopenias coming under the inclusion criteria. 317 cases were of Bicytopenia and 97 cases were of Pancytopenia. The most commonly observed bicytopenia is anemia with thrombocytopenia followed by anemia with leukopenia and leukopenia with thrombocytopenia. The mean age of cases in our study population was 56 years with a male preponderance. In pancytopenia, there was strong correlation between hemoglobin with total count and platelet count. We also observed that the most common cause of pancytopenia was megaloblastic anemia followed by multiple myeloma. The most common cause of bicytopenia was infections followed by Multiple myeloma and Myeloproliferative Neoplasm. **Conclusion**: A strong clinical suspicion with the presence of leukocytosis, life threatening to severe anemia, leukoerythroblastic blood picture, and the presence of blasts almost always warrants a bone marrow aspiration. The absence of the same excludes the necessity for bone marrow examination. From our research, we infer that a case of chronic bicytopenia not improving on treatment must be evaluated for hematological malignancies. Many indolent hematological malignancies in our study presented with mild anemia or mild bicytopenia. 8.2 % of cases turned out to be indolents hematological malignancy such as Myeloproliferative neoplasm, Myelodysplasia etc. Progressive anemia with thrombocytopenia followed by leucopenia must be subjected to bone marrow examination. We submit that bone marrow examination may be performed in chronic bicytopenia cases even if there is only mild anemia, and a comprehensive interdisciplinary approach inclusive of flowcytometry, molecular genetic analysis must be adopted so that even the mildest possibility of hematological malignancy is not missed.

Keywords: Pancytopenia, Bicytopenia, Hematological Malignancies, Clinical Profile.

INTRODUCTION:

Pancytopenia is a hematologic condition characterized by a decrease in all three peripheral blood lineages. Bicytopenia is the condition where there is a decrease in two of the hematopoietic lineages [1-2]. It is not a disease entity on its own but a variety of cytopenias originating from various disease processes. Cytopenias are characterized by a reduction in hemoglobin level less than 12 g/dL in women; 13 g/dL in men, decrease in platelets count less than 1, 50,000 per mcL, and decreases in leukocyte count less than 4000 per mcL.[1-3] The causes of cytopenia can vary among different populations based on characteristics like age, gender, nutrition , geographical location ,living standards, as well as exposure to infections and drugs.[4] India being a developing country, nutritional deficiency (Iron, Folate, B12) is a major cause for cytopenia. Awareness, access and availability of healthy nutritious food remain a major problem in India and is still a process under implementation. Environment also plays a significant role. Being a tropical country with dense forests and having a humid atmosphere, India is home to many infectious diseases. India is home to a very large population and we are yet to improve our socio- economic conditions and raise the standard of living. Mostly the patients are rural residents with poor economic status. Bicytopenia is the condition where there is decrease in two blood lineages. The most commonly observed bicytopenia is anemia with thrombocytopenia followed by anemia with leukopenia and leukopenia with thrombocytopenia. There is a male preponderance. It is understood that bicytopenia is more common due to non malignant causes than malignant causes in India. Literature indicates that bicytopenia may also be due to Aplastic anemia and Acute leukemias such as Acute Lymphoblastic Leukemia followed by Acute myeloid leukemia. Myeloproliferative/ Myelodysplastic syndromes, lymphoproliferative neoplasms and plasma cell neoplasms are other heterogeneous groups of disorders which are also characterized by peripheral blood cytopenias. [5- 7]

Some indolent malignancies may take years to be symptomatic and only when they transform to acute leukemia where much aggressive treatment may be required. Predominant non- malignant cause is megaloblastic anemia followed by Immune Thrombocytopenic Purpura, Alcoholic disease/ Hypersplenism, infections, inadequate nutrition due to other chronic diseases.

The mechanism of development of cytopenia is due to two reasons. 1) Ineffective bone marrow production which may be due to marrow failure syndromes 2) Peripheral destruction of cells which may be immune mediated or by sequestration of cells such as in Hypersplenism. Since the cause and clinical features is the most important determinant in formulating a treatment plan and predict the prognosis of patients with pan and bicytopenia, we aimed to develop a thorough clinical and etiological profile of patients with bicytopenia and pancytopenia coming to our tertiary care centre.

MATERIALS AND METHODS:

The study was an observational descriptive study undertaken in the Department of Pathology in collaboration with the department of Oncology during a period of 3 years (January 2020 - January 2023) in a tertiary care hospital in Ernakulam, Kerala, India. All available reports of pancytopenia and bicytopenia were retrieved from the study period. The complete blood count, peripheral smear and bone marrow reports were taken. On the basis of the severity of anemia the cases were further classified into mild, moderate, severe and life threatening. Relevant clinical details such as history, presenting complaints and symptoms, physical examination findings were noted from patient records. Relevant hematological investigations also were noted.

Inclusion Criteria:

Adult population that is age more than 18 yrs , a hemoglobin cut off for males is less than 13.0 gm% and for females less than 12 gm% ,a total white blood cell of less than 4000/uL and platelet count less than 1,50,000/uL were included in the study.

Exclusion Criteria:

Patients on chemotherapy and children (age less than 18 yrs) were excluded from the study.

Statistics:

The data retrieved was tabulated and represented in percentages, measures of central tendency and analyzed statistically for correlation between the severity of anemia and disease outcome using T - Test and ANOVA interpretation. The descriptive statistics for the tests are represented as graphs and charts.

RESULTS:

During the period of January 2020 to December 2022, we encountered 414 cases of cytopenias coming under the inclusion criteria. 317 cases were of Bicytopenia and 97 cases were of Pancytopenia. Majority [90 %] of these patients were residents of Ernakulam district, Kerala, India. The mean age of cases in our study population was 56 yrs.

[Table.1]. There were 232 males and 165 females (M:F =1.4:1). The most common age group was those between 59-68 years of age.

Table: 1. Distribution of age in the study population

AGE	FREQUENCY
18-28	34
29-38	39
39-48	56
49-58	75
59-68	**94**
69-78	75
79-88	34
89-98	7
TOTAL	414

Table: 2. Sex distribution in study population in pancytopenia

Category			Total
	Male	Female	
Life Threatening	7	13	20
Severe	18	6	24
Moderate	16	9	25
Mild	15		28
Total	**56**	**41**	**97**

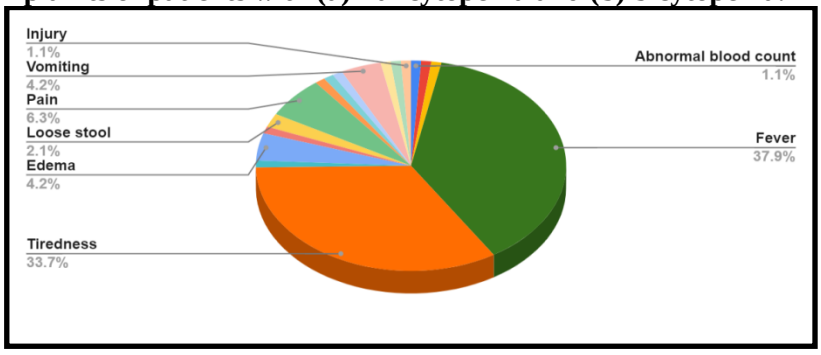
Table: 3. Sex distribution in study population in bicytopenia

Category				Total
	Male	Female	Missing	
Life Threatening	8	8	0	16
Severe	17	17	3	37
Moderate	48	41	1	90
Mild	103	58	13	174
Total	**176**	**124**	**17**	**317**

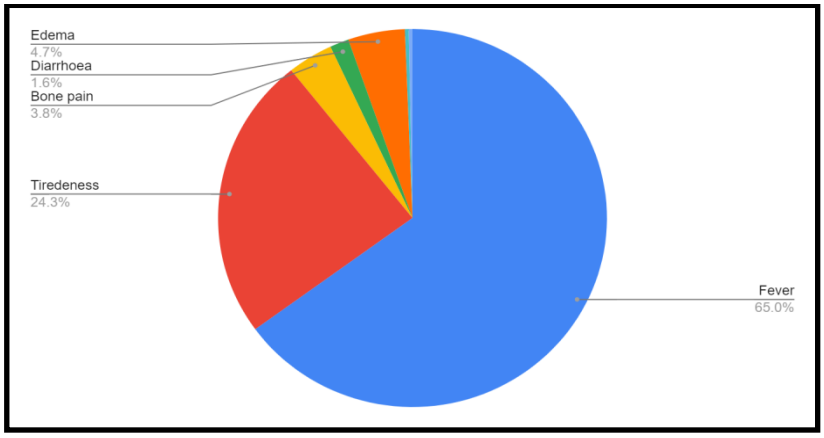
The common presenting complaints were fever (37.9%) followed by weakness/tiredness (33.7%), pain (6.3%), edema (4.2%), vomiting (4.2%) and lastly injury (1.1%). Clinical examination, the majority of the patients showed hepatomegaly, followed by splenomegaly and lymphadenopathy [Diagram .1 (a,b)].

Diagram .1 : Presenting complaints of patients with (a) Pancytopenia and (b) bicytopenia.

(a)



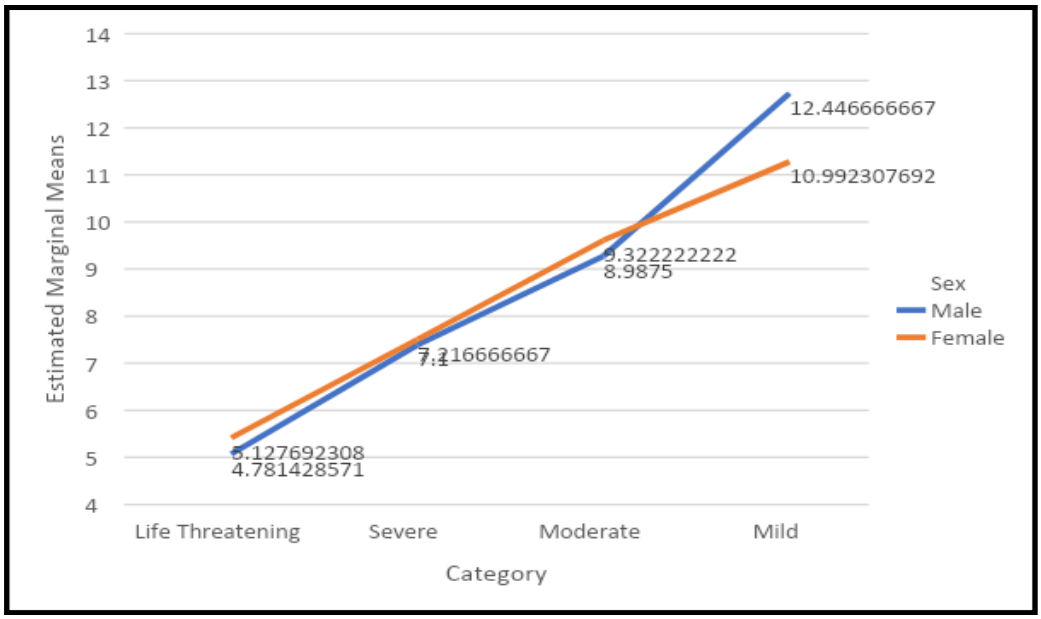
(b)



PANCYTOPENIA :

The hemoglobin values varied from 5.3 g/dl to 11.8 g/dl. The average hemoglobin of males was 10 g/dl and females were 8.95 g/dl. Average value of WBC count was 5,689.52/ul in males and 5,578.57 /ul in females. And average platelet count in males was 83,270.27/ul and 95,897.53 /ul in females. [Diagram . 2]

Diagram.2: Difference between the hemoglobin (gm%) between males and females across various categories in pancytopenia showed a positive correlation.



On analyzing the correlation between different categories of anemia in pancytopenia , as the anemia progressed from moderate to severe, it was observed that, initially there is associated drop in platelet count and as anemia further progressed from severe to life threatening in addition to the gradual thrombocytopenia, there was progressive leukopenia as well. From this observation, it may be inferred that as one monitors the cytopenias over a period of time, progressing of anemia followed by thrombocytopenia and later by leukopenia it may be construed that such progression indicates poor patient prognosis. We observed that in the pancytopenia cases, there is a positive correlation between Hemoglobin and Leukocyte count. The trend of leukocyte drop is similar to that of Hemoglobin drop. Also the average platelet count was twice more in females than in males, thus one must not be misled by a spurious platelet count in females and undermine the severity of the disease situation in women.

BICYTOPENIA:

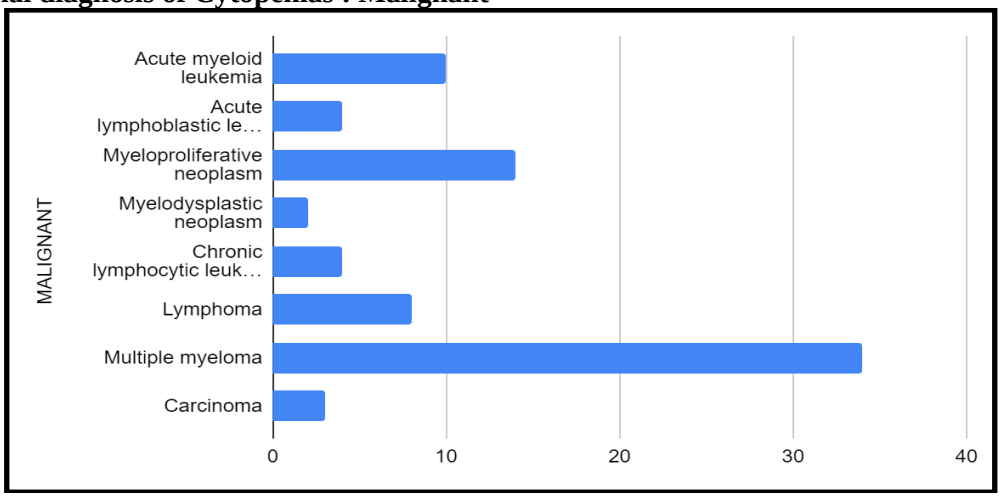
On analyzing the correlation between four categories of anemia in bicytopenia , it was observed that the values of Hb between males and females was minimal in moderate and nil in severe category. However, it showed a sharp difference in mild and life threatening categories. We infer that in bicytopenia there is no definite correlation between the parameters across four categories.

Causes of Cytopenias:

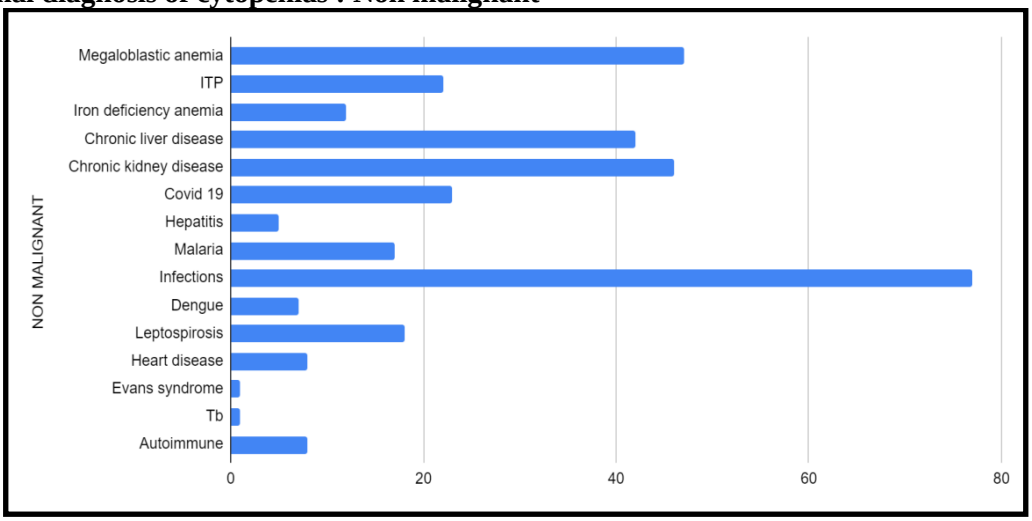
Most common malignant causes of cytopenias in our study were Multiple Myeloma (34, 42.5%) followed by Myeloproliferative Neoplasm (14, 16.09% %), followed by Acute myeloid leukemia (10, 11.49% %),

Non- Hodgkin's Lymphoma(8,9.19% %). We had 4 cases of Acute Lymphoblastic Leukemia (4.59 %) and 4 cases of Chronic Lymphocytic Leukemia (5.59%) and lastly two cases of Myelodysplastic Neoplasm (2.29%). [Diagram. 3] Among the non-malignant category, the most common cause for bicytopenia and pancytopenia in our study were infections most common being the infamous Covid 19 (23,6.88%) , Leptospirosis (18,5.38%), Malaria (17,5.08 %) ,Dengue (7, 2.09%), Hepatitis(5,1.4%), one case of Brucellosis (0.29 %)and Tuberculosis (0.29%). 77 cases were treated for various other bacterial and viral infections (23.05 %). If we exclude infections, the most common case of bicytopenia and pancytopenia is due to megaloblastic anemia (47,14.1 %) followed by chronic systemic diseases such as chronic kidney disease (46,13.77%) and chronic liver disease (42, 12.57%). Iron deficiency anemia constituted (12, 3.59 %) , autoimmune disease (8, 2.39 %) , 8 cases of heart disease (2.39 %) and one case of Evans syndrome (0.29%).[Diagram. 4]

Diagram . 3 Final diagnosis of Cytopenias : Malignant

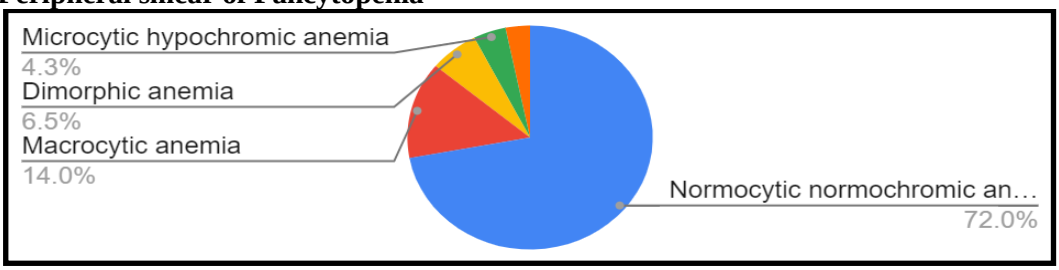


Digram. 4 : Final diagnosis of cytopenias : Non malignant



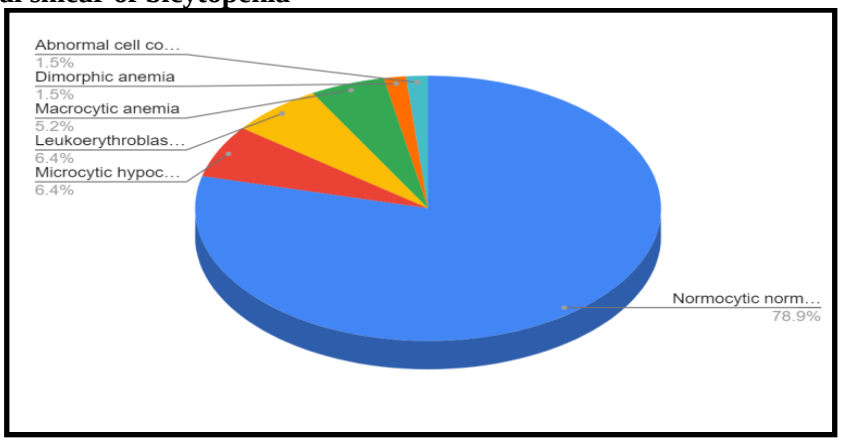
Out of 97 cases of pancytopenia, the peripheral smear showed predominantly normocytic normochromic anemia (72.0%) followed by macrocytic anemia (14.0%), dimorphic anemia (6.5%) and lastly microcytic hypochromic anemia (4.3%).[Diagram 5]

Diagram. 5: Peripheral smear of Pancytopenia



Out of 317 cases of bicytopenia, peripheral smear showed predominantly normocytic normochromic anemia (78.9%) followed by leukoerythroblastic blood picture and microcytic anemia (6.4%), macrocytic anemia (5.2%) and lastly dimorphic anemia and abnormal cell count(1.5%) [Diagram. 6].

Diagram. 6 : Peripheral smear of bicytopenia



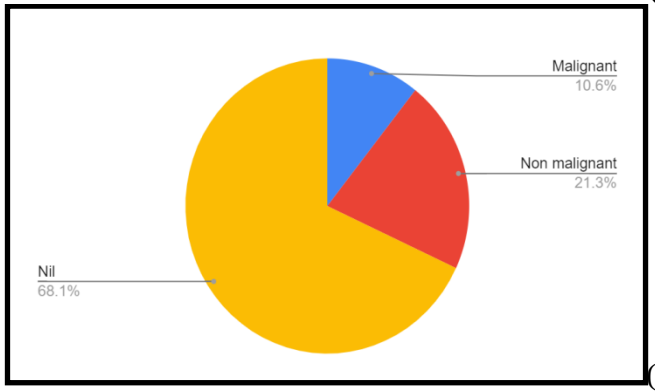
Patients were classified into four categories based on the severity of anemia. In life threatening category there were 20 cases (21.9%) of pancytopenia and 16 cases (5.01%) bicytopenia, in severe category there were 24 cases (24.7%) of pancytopenia and 37 cases(11.6%) of bicytopenia, in moderate category there were 25 cases(25.7%) of pancytopenia and 90 cases (28.4%) bicytopenia, in mild, there were 28 cases (28.7%) of pancytopenia and 174 cases (54.7%) of bicytopenia.[Table . 4]

Table . 4 Showing the Cases Distributed Against the Categories

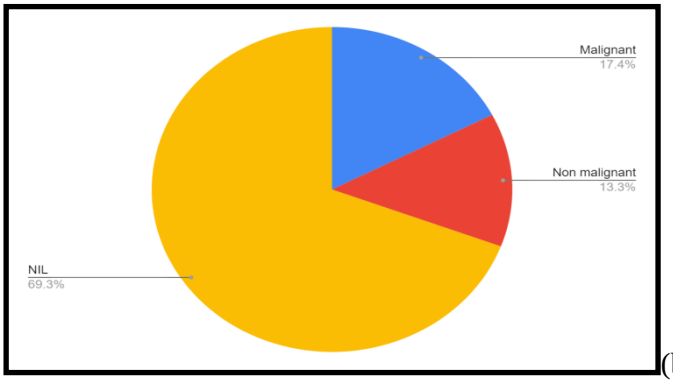
CATEGORY	PANCYTOPENIA	BICYTOPENIA	MALIGNANT
Life threatening anemia (6.5 gm%)	20 cases (21.9%)	16 cases (5.01%)	33 %
Severe anemia (6.5 to 8.0 gm%)	24 cases (24.7%)	37 cases (11.6%)	32.7 %
Moderate anemia (8.0 to 10.5 gm%)	25 cases (25.7%)	90 cases (28.4%)	18.2 %
Mild anemia (10.0 to 13.0 gm %)	28 cases (28.7%)	174 cases (54.7%)	8.4 %

In our study, a total of 131 bone marrow aspiration and biopsy were done out of these 131 cases, the majority of patients had hypercellular marrow (70 %) followed by (15 %) with hypocellular marrow and (5%) Normocellular marrow. The most common cases were that of hematolymphoid malignancy 76 cases (58%) and Multiple myeloma 34 (26.0%) was the most common. Following myeloma we had myeloproliferative neoplasms 14 (10.7%), followed by lymphoproliferative neoplasm 12 (9.1%). Acute leukemia constituted 7 cases (5.3%) with predominantly Acute Myeloid Leukemia (3, 3.9 %) and one case of Acute Lymphoblastic Leukemia (0.8%). Aplastic / hypoplastic marrow were seen in 7 cases (5.3%). Two cases were Myelodysplastic Neoplasm (1.5%) with trilineage dysplasia, in which one exhibited SF3B1 Mutation with Monosomy 7. Other case exhibited ring sideroblasts of 10 % and features of Hemophagocytosis [Figure1]. In lymphoproliferative neoplasm, 6 cases were B cell Non Hodgkin's lymphoma and 2 cases were T cell lymphoma. One case of T cell lymphoma showed features of cutaneous T cell lymphoma (Mycosis fungoides). There were 4 cases of Chronic Lymphocytic Leukemia. [Table . 4]

Table 5 : Bone Marrow Examination Undertaken in Our Institution (a) Pancytopenia (b) Bicytopenia

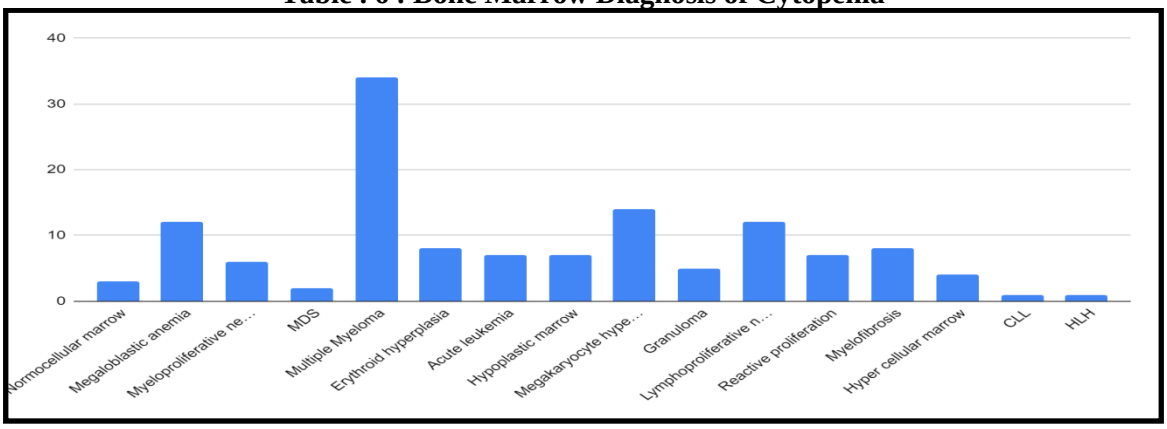


(a)Pancytopenia



(b) Bicytopenia

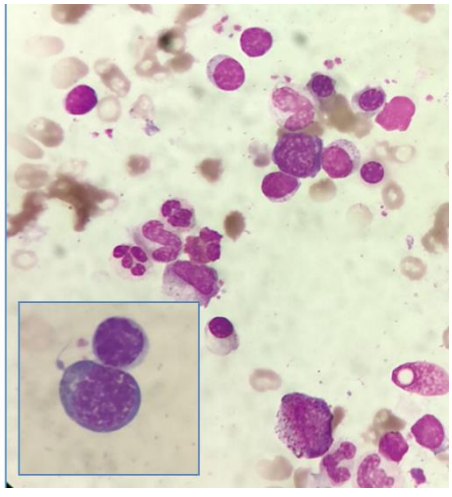
Table . 6 : Bone Marrow Diagnosis of Cytopenia



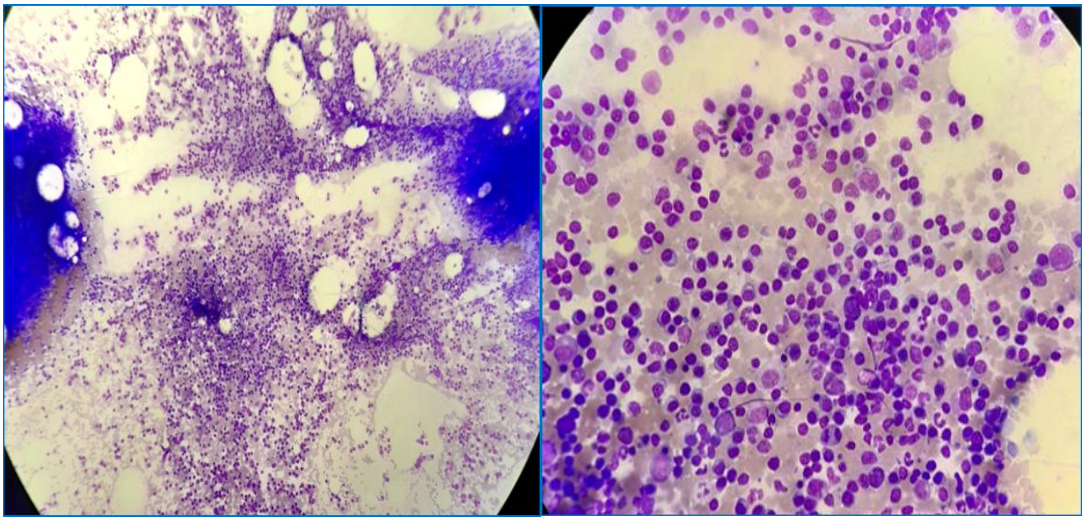
Karyotyping was done by cytogenetic analysis of bone marrow aspirate samples. Overwhelming majority (80%) had a normal karyotype. In myeloproliferative neoplasm, we had 4 cases of chronic myeloid leukemia ,8 cases of primary myelofibrosis, 1 case of essential thrombocythemia and 1 case of polycythemia vera. All cases were diagnosed with flow cytometry and molecular genetic analysis. All cases of CML showed BCR-ABL 1 rearrangement. In primary myelofibrosis,5 cases were positive for JAK2 mutation and 3 were positive for CALR mutation. None showed MPL mutation. Other 55 cases (42%) of bone marrow cases were non malignant. The most common cause was Megaloblastic anemia - 12(9.1%), followed by Megakaryocyte Hyperplasia/ ITP - 14 , 10.6%), followed by erythroid hyperplasia - 8(6.1%). We also had 7 cases of trilineage hematopoeisis (5.3%). We had one case of Hemophagocytic Lymphohistiocytosis (HLH) (0.7%) as well. Cytogenetics was undertaken in cases of myeloproliferative neoplasms and mostly for CML and suspected cases of primary myelofibrosis. Amongst the cases of primary myelofibrosis, (58.2%) genetic abnormality encountered was **JAK2 mutation**, followed by CALR mutation. [Table 7.]

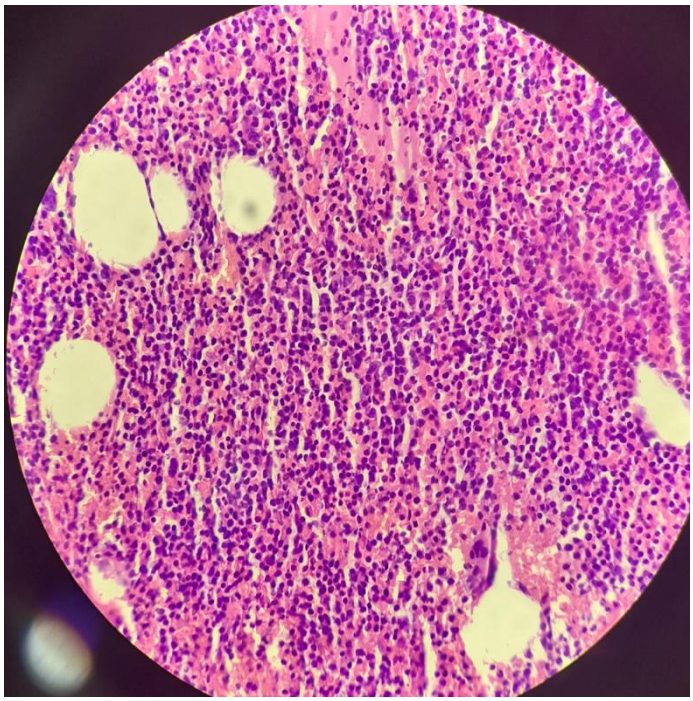
Table . 7 : Ancillary Studies Undertaken in Hematological Malignancies.

DISEASE	FLOW CYTOMETRY	GENETICS	FREQUENCY
Chronic Myeloid Leukemia	Not done	BCR-ABL Rearrangement	4
Myeloproliferative neoplasm (Primary Myelofibrosis)	Not done	1.**JAK-2 Mutation** 2.CALR Mutation 3.MPL Mutation	**7** 3 0
Myelodysplastic neoplasm	11% Myeloblast and 12% Monocyte	SF3B1 Mutation and Monosomy 7	1
Chronic lymphocytic leukemia	92% cells positive for CD20,CD23.CD43,CD 11c,ROR 1	Trisomy 12p.11.1-q11	2
Acute myelomonocytic leukemia	8.5% Myeloblast (positive for CD117,CD34,CD13,C D33,MPO,and HLA-DR) 20% atypical monocyte (positive for CD11c,CD13,CD33,C D64 and HLA-DR) 13.5% mature monocyte (positive for CD14.)	Not done	2
Acute lymphoblastic leukemia	52% lymphoblast positive for CD3,CD5,CD7,CD 23, CD33	Not done	1

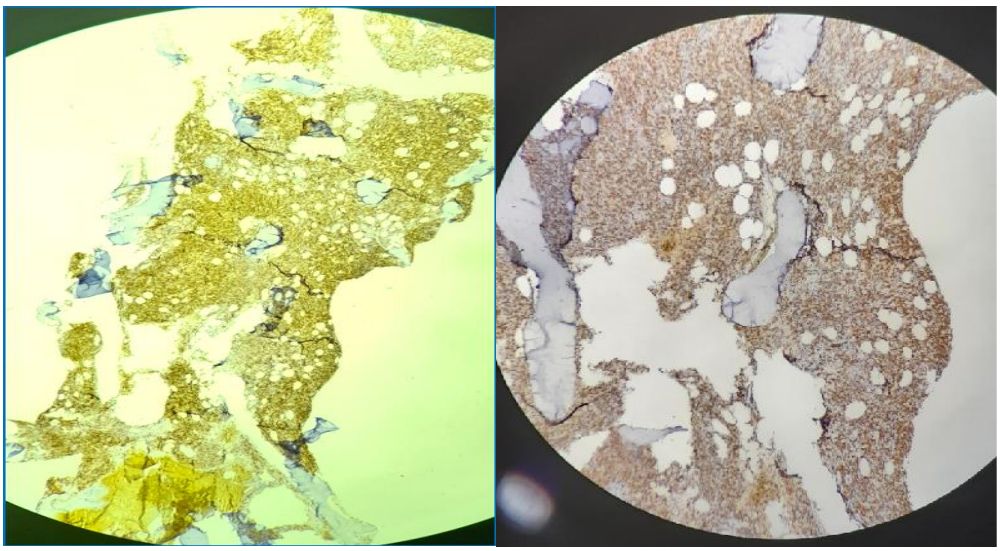


[Figure: 1. Bone marrow showing megaloblast and giant myelocytes and metamyelocytes. A case of Megaloblastic anemia.]





[Figure. 2 Bone marrow of a 58 yr old woman with Ig G Lambda light chain disease, marrow is hypercellular marrow with lymphoplasmacytic proliferation and showed clonal restriction for Lamda.]



[Figure . 3 : Immunohistochemistry Showing CD 138 Positivity and Lambda Restriction]

Table: 8. Comparison of Causes of Pancytopenia Sited in Different Studies Across the World.

NAME	COUNTRY	YEAR	NO.OF CASES	MOST COMMON DIAGNOSIS	2ND MOST COMMON DIAGNOSIS
Bae et.al	Korea	2015	1,580	Acute myeloid leukemia(25.9%)	Infections(25.6%)
Yongping Li et.al.	China	2015	25	Megaloblastic anemia	Aplastic anemia(20%)
Nell et.al.	Africa	2017	673	Chemotherapy	Sepsis (18%)
Batool et.al.	Pakisthan	2018	237	Megaloblastic anemia (27%)	Aplastic anemia (15.6%)
Chandra et.al	India	2019	131	Megaloblastic anemia (25%)	Acute leukemia (19%)
Carretero et al	Mexico	2019	109	Myelodysplastic syndrome (20.25%)	Megaloblastic anemia(18.3%)
Present study	India	2023	414	Megaloblastic anemia (11.35%)	Multiple Myeloma (8.2 %)

DISCUSSION:

Cytopenia, a reduced count of blood cells manifesting as anemia, neutropenia, and/or thrombocytopenia. It is frequently associated with many medical conditions. However, a cytopenia may not be accompanied by a known determinant and in some of these cases, may be a precursor to pre-malignancies or hematologic cancers. [7]. Mild cytopenia is a common manifestation of various illnesses usually due to infections or nutritional deficiencies. In developing countries these two causes are always a problem. People from poor socio-economic classes neglect their personal health as they are trying to earn a living for their family. In routine clinical practice, one tends to overlook cases of mild cytopenias or bicytopenia as the same rarely present as malignancy. Over a period of three years, we studied over 414 cytopenia (bicytopenia - 76.57% and pancytopenia - 21.73%) cases on patients who visited our hospital for treatment. Most patients presented with fever, weakness/ tiredness or were treated for an ongoing chronic disease which was similar to the elaborate study conducted [8] . The second most common cause was megaloblastic anemia(47,11.35%) This is similar to other studies conducted around the world which show infections and megaloblastic anemia as the main cause for pancytopenia, followed by aplastic anemia.

In our study, the mean age was 56 years, suggest that our patient population is middle age population compared to few previous studies. Most patients were in age group of (48-58).This is similar to a study conducted by Gayathri Et al, where the mean age was found to be 42 years.

In 2011, Yoojoum Lim Et al observed the correlation between iron deficiency anemia and leucopenia. The severity of leukopenia correlates with the decrease of hemoglobin in a dose -dependent manner. Among the WBC subsets, lymphocyte count is usually affected. In our study, we observed a positive correlation between severity of anemia, thrombocytopenia and leukopenia. As the anemia progresses, there is an initial fall in platelets followed by leukocytes. This observation may be useful while monitoring a case of pancytopenia. [9]

In cases of pancytopenia as the anemia progresses, with associated gradual thrombocytopenia followed by gradual leukopenia this must alarm the physician/clinician of an underlying hematological malignancy. Amongst hematological malignancies, we encountered mostly Multiple Myeloma (42.5%) out of which 68 % showed Kappa restriction and remaining 32 % showed Lambda restriction. According to WHO, myeloma is the clonal neoplastic proliferation of plasma cells that excrete any one form of protein. We had one case of Ig G Lambda light chain disease, which showed a hypercellular marrow with lymphoplasmacytic proliferation and showed clonal restriction for Lamda.(Fig .1). The serum showed abnormally high levels of Lambda (11500ug). There was no detectable M protein, Kappa was 5 ug. In a case series by B Sridevi et al, all 10 cases of multiple myeloma presented with pancytopenia. The cause of cytopenia may be due to suppression of normal haematopoiesis by the neoplastic cells resulting in

destruction of bone, renal failure and recurrent infections. Although myeloma has an indolent course, plasmablastic transformation requires aggressive treatment. (figure. 2) Development of primary amyloidosis is one complication. (fig. 3)

The second common cause for cytopenia in our study was myeloproliferative neoplasm. They almost always present with bicytopenia or pancytopenia. Chronic myeloid leukemia (CML) presents with anemia and marked leukocytosis and thrombocytosis. [18] In our study few cases showed mild leukocytosis without thrombocytosis but showed BCR-ABL rearrangement. CML may present at any stage of the disease. One must count the blast percentage in order to rule out acute leukemia/ excess blasts. (Fig. 4)

According to the fifth edition of World Health Organisation classification of hematolymphoid tumors: Myeloid and Histiocytic/Dendritic neoplasm, the percentage of blast is given prime importance. Inclusion of Flow Cytometry with molecular genetic analysis is the latest diagnostic criteria and has replaced earlier concepts of cytopenias versus presence of blasts/leukemoid reaction and organomegaly. Myeloid neoplasm is now a spectrum ranging from indolent myeloproliferative neoplasm/MDS at one end and acute blastic leukemia at the other extreme. The genetic profile is different.[10 - 12]

Other myeloproliferative neoplasms include Primary Myelofibrosis, Essential Thrombocythemia and Polycythemia Vera. Our study showed 14 Cases of MPN excluding CML. All cases were diagnosed with cytogenetic analysis. The predominant mutation turned out to be JAK 2 mutation, followed by CALR mutation (PMF).

Among acute leukemias, AML is more common than ALL. We had two cases of acute leukemia diagnosed on bone marrow and flow cytometry. Among the Non-Hodgkin's lymphomas, we had more B cell lymphomas and one case of T cell lymphoma. All lymphomas were diagnosed with the help of immunohistochemistry. Two cases showed leukemic transformation into blood.

Most common non- malignant causes of cytopenia in our study were due to infections, such as Covid, leptospira, malaria, dengue, hepatitis, brucellosis and tuberculosis. If we exclude infections, the most common cause for cytopenia is megaloblastic anemia followed by chronic systemic illnesses such as chronic liver disease and chronic kidney disease.

Clinical Approach to Pancytopenia:

Pancytopenia can be associated with multiple disease conditions.a proper history physical examination and focused investigations will help in getting a timely diagnosis and early intervention. We commonly encounter diseases resulting in the replacement of bone marrow by hematologic malignancies, metastatic malignancies, myelofibrosis, infectious disease. Non-malignant causes of of bone marrow aplasia such as nutritional deficiencies of vitamins, aplastic anemia, viral infections, Immune mediated cell destruction long term medications is yet another cause. Blood cell destruction or sequestration in DIC, TTP, and ineffective hematopoiesis can cause excessive destruction while sequestration in spleen seen in hypersplenism of any cause. Occasionally, all these mechanism will co-exist as in lymphoma related immune destruction, marrow infiltration, hypersplenism.

Evaluation of Pancytopenia:

Clinical evaluation starts with a routine detailed history and clinical examination supplemented by relevant investigations. History include disease course with severity and comparing with relevant prior investigations. Recurrent infections, symptoms suggestive of anemia, constitutional symptoms, features of organ malignancies, bleeding manifestations other co-morbid conditions, medications including alternative medicines, personal and occupational and dietary history is also noted. Family history is mandatory to rule out inherited malignancies and coagulation disorders. Physical examination we take note of rashes, oral lesions, lymphadenopathy, splenomegaly, hepatomegaly and or any incidental lumps.

Investigations include all above mentioned routine investigations inclusive of hematology and biochemistry. All pancytopenia cases under go bone marrow examination, preferably with flowcytometry and molecular genetic analysis where ever feasible. Standard indications to do a bone marrow examination in clinical setting is unexplained anemia ,leukopenia, thrombocytopenia, pancytopenia, presence of blast in peripheral smear, teardrop cells, hairy cells etc. All suspected cases of Multiple myeloma, staging for lymphoma, unexplained splenomegaly, PUO evaluation and also as part of amyloidosis workup.

In our research, we came across a variety of diseases ranging from malignant to non malignant. Pancytopenia with severe anemia showed highest chances of hematological malignancy (13.40%) and in almost always a bone marrow is performed. Lesser the degree of anemia, lesser malignancies were encountered and lesser bone marrows were performed. Throughout our research we observed that more number of bone marrow examinations were performed under severe and life threatening anemia, which is also the accepted clinical practice. In mild and moderate anemia the frequency of bone marrow examination was less, unless it was associated with obvious clinical and pathological features.

A strong clinical suspicion with the presence of leukocytosis, life threatening to severe anemia, leukoerythroblastic blood picture, and the presence of blasts almost always warrants a bone marrow aspiration. The absence of the same excludes the necessity for bone marrow examination. From our

research, we infer that a case of chronic bicytopenia not improving on treatment must be evaluated for hematological malignancy. Many indolent hematological malignancies in our study presented with mild anemia or mild bicytopenia. 8.2 % of cases turned out to be indolents hematological malignancy such as Myeloproliferative neoplasm, Myelodysplasia etc. Bone marrow examination is not required in such cases as the patients are generally healthy. As far as bone marrow examination is concerned there must be an absolute indication to perform the same as it is very inconvenient and traumatizing to the patients.

CONCLUSION:

A combination of a strong clinical suspicion, accurate pathological diagnosis and relevant, focused work up is essential to elucidate the correct underlying diagnosis in patients with bicytopenia and pancytopenia. The presence of moderate to severe leukocytosis, life threatening to severe anemia, leukoerythroblastic blood picture, and the presence of blasts almost always warrants a bone marrow aspiration. The absence of the same excludes the necessity for bone marrow examination. Our series have inferred that the most common cause of pancytopenia is Megaloblastic anemia and for bicytopenia it is Multiple Myeloma. From our research, we infer that a case of chronic bicytopenia not improving on treatment must be evaluated for hematological malignancies. We submit that bone marrow examination may be performed in chronic bicytopenia cases even if there is only mild anemia, and a comprehensive interdisciplinary approach inclusive of flowcytometry, molecular genetic analysis must be adopted so that even the mildest possibility of hematological malignancy is not missed.

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Limitations of the Research:

The research is a pilot study undertaken in a small sample size and most of the bone marrow diagnosis with flowcytometry and molecular genetics was outsourced to another NABL accredited lab.

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