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Study of Bone Marrow Changes in 106 Cases with Pancytopenia, Bicytopenia

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Abstract

Pancytopenia and Bicytopenia are hematological findings which can occur from various etiological factors mainly involving the bone marrow. In our study of 106 cases of Pancytopenia (63 cases, 59.43%) and Bicytopenia (43 cases, 40.56%), megaloblastic anemia was the commonest finding which reflects the nutritional anemia in our country which can be corrected easily, followed by hypoplastic marrow, erythroid hyperplasia and HIV infection. Most of the patients were in 21-30 yrs of age group 26 cases (24.52%). Males were more 61 cases (57.54%) than females 45 cases (42.45%). In our study, HIV infection was found in 13 cases and 1 case of HBs Ag positive. HIV infection is emerging as another leading cause for Pancytopenia and Bicytopenia. Thrombocytopenia cases were more in our study because of ITP and Infection associated thrombocytopenia (IAT), due to Dengue out break during our study period. Final diagnosis requires morphological examination of marrow by doing bone marrow aspiration along with bone marrow biopsy, clinical examination in association with Vit B12 and folic acid levels, enzyme assays, serology, electrophoresis, markers etc along with radiological evaluation is needed for optimization of results & proper diagnosis in relevant cases.

Keywords: Bicytopenia; Bone Marrow; HIV; Megaloblastic Marrow; Pancytopenia.

Introduction

Pancytopenia is defined by reduction of all three formed elements of blood below the normal reference [1]. The criteria applied for pancytopenia were Haemoglobin (Hb) <10 g/dl, Total leucocytes count (TLC) <4000/cumm, Platelet count <1 lakhs/cumm [1]. Presence of any above 2 criteria was applied for Bicytopenia. The bone marrow examination is extremely helpful in evaluation of pancytopenia, bicytopenia. The bone marrow aspiration study was carried to identify the underlying etiopathology and various morphological features of bone marrow in cases of pancytopenia, bicytopenia and HIV infected patients.

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Material and Methods

This observational study of 106 cases were studied during the period, January 2013 to December 2014, in the department of pathology, Bowring and Lady Curzon Hospital, Bangalore. Patients of all age groups admitted in Hospital , with hematological diagnosis of Pancytopenia, Bicytopenia and patients with HIV infections were included in the study.

Selection of Cases

Patients of all age groups admitted in Bowring and Lady Curzon Hospital, Bangalore, with diagnosis of pancytopenia, bicytopenia and referred cases with HIV infection were taken for the Bone marrow aspiration study. The following criteria were applied for pancytopenia Haemoglobin(Hb) <10 g/dl, Total leucocyte count (TLC) <4000/cumm, Platelet count

<1 lakh/cumm [1]. Presence of any above 2 criteria were applied for Bicytopenia.

Patients who did not give consent for bone marrow aspiration were excluded from the study.

Informed Consent was taken from all the patients after explaining the procedure to the patient and their relatives in case file.

Procedure

After taking all aseptic precautions bone marrow aspiration was performed from posterior superior iliac spine in adults and tibia in children with bone marrow aspiration needle (Klima needle Adults- 18G and Pediatrics 16 G). Routine stains like Leishman's stain were used and special stains like reticulin, and Prussian blue stains were used as per requirements. Peripheral smears were also studied after staining with Leishman's stain along with complete blood count (CBC).

Bone marrow biopsy were done in cases of dry tap or aspirates diluted with blood for confirmation of diagnosis.

Results

The total number of cases studied were 106 cases.

In our study 63 cases (59.43%) were Pancytopenia, 43 cases(40.56%) were of Bicytopenia, out of which13 cases (12.26%) were of HIV infected patients and one case (0.94%) of HBsAg infected patient . Among 106 patients the age ranged from 8 months to 72 yrs (Table 1). Most of the patients were in 21 – 30 yrs age group.

45 cases (42.45%) were females and 61 cases (57.54%) were males.

Table 1: Age distribution of cases

Age	No of cases	Percentage
0-10 yrs	08	7.54%
11-20 yrs	14	13.20%
21-30 yrs	26	24.52%
31-40 yrs	23	21.69%
41-50yrs	14	13.20%
51-60yrs	10	9.43%
61-70 yrs	07	6.60%
>70yrs	04	3.77%

Table 2: Bone marrow aspiration findings in 106 cases

Diagnosis	Pancytopenia		Bicytopenia	
	No of cases	Percentage	No of cases	Percentage
Megaloblastic anemia	16	25.39	06	13.95
Erythroid hyperplasia	13	20.63	04	9.30
Hypoplastic marrow	13	20.63	01	2.32
Normocellular marrow	04	6.34	04	9.30
Myelodysplastic syndrome	06	9.52	04	9.30
Acute lymphoblastic leukemia	02	3.17	Nil	Nil
Acute myeloid leukemia	02	3.17	02	4.65
Non hodgkins lymphoma	02	3.17	Nil	Nil
Plasmacytosis	01	1.58	02	4.65
Myeloma	Nil	Nil	03	6.97
Tuberculosis	Nil	Nil	01	2.32
Storage disorder	Nil	Nil	02	4.65
Pure red cell aplasia	Nil	Nil	01	2.32
Refractory anemia with MDS	03	4.76	01	2.32
Increased megakaryopoiesis	01	1.58	09	20.93
Reactive Eosinophilia	Nil	Nil	01	2.32
Refractrory anemia	01	1.58	Nil	Nil
Inconclusive	01	1.58	Nil	Nil

Table 3: Causes of Pancytopenia in various studies

S. No	Study	Country	Year	No of cases	Commonest cause	Second most common cause
1	Khunger J M. et al[5]	India	2002	200	Megaloblastic anemia(74%)	Aplastic anemia(14%)
2	Mobina Ahsan Dodhy et al[6]	Pakistan	2005	392	Megaloblastic anemia(35.95%)	Hypersplenism
3	Jha et al[7]	Nepal	2008	148	Hypoplastic anemia(29.5%)	Megaloblastic anemia(23.64%)
4	B N Gayathri and Kadam atyanarayan Rao[8]	India	2011	104	Megaloblastic anemia(74.04%)	Aplastic anemia(18.26%)
5	Verma Nidhi et al[9]	India	2012	72	Megaloblastic anemia(40.3%)	Aplastic anemia
6	Sachin D. Tonape[2]	India	2013	210	Megaloblastic anemia(65.71%)	Aplastic anemia
7	Present study	India	2014	106	Megaloblastic anemia(25.39%)	MDS ,Hypoplastic anemia(20.63%) & erythroid yperplasia(20.63%)

Table 4: Bone marrow findings in 13 HIV patients

Diagnosis	Pancytopenia	Bicytopenia	Percentage
Hypoplastic marrow	03	01	30.76%
Erythroid hyperplasia	02	Nil	15.38%
Megaloblastic anemia	01	Nil	7.69%
Normal marrow	02	Nil	15.38%
Myelodysplastic syndrome	02	Nil	15.38%
Plasmacytosis	01	Nil	7.69%
Inconclusive	01	Nil	7.69%

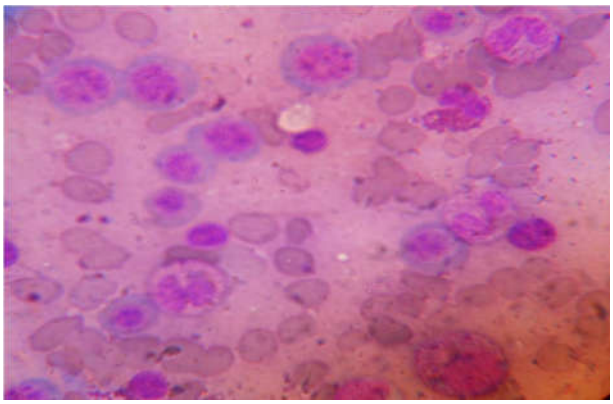

Fig. 1: Bone marrow aspiration showing megaloblastic change. (100x)

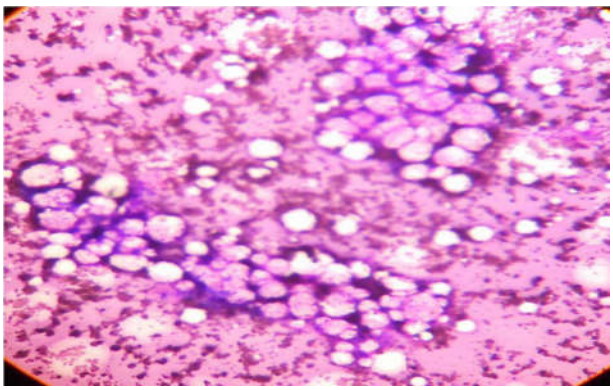

Fig. 2: Bone marrow aspiration showing hypocellular marrow

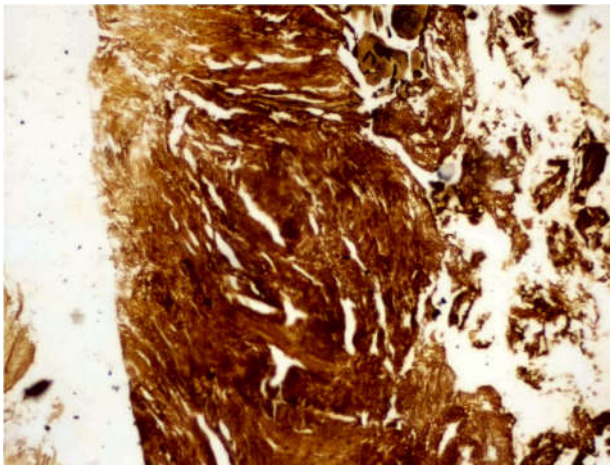

Fig. 3: Reticulin staining showing fibro collagenous fibres

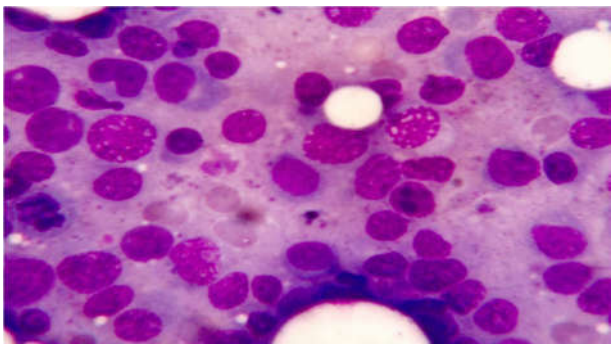

Fig. 4: Bone marrow aspiration showing plasmacytoma

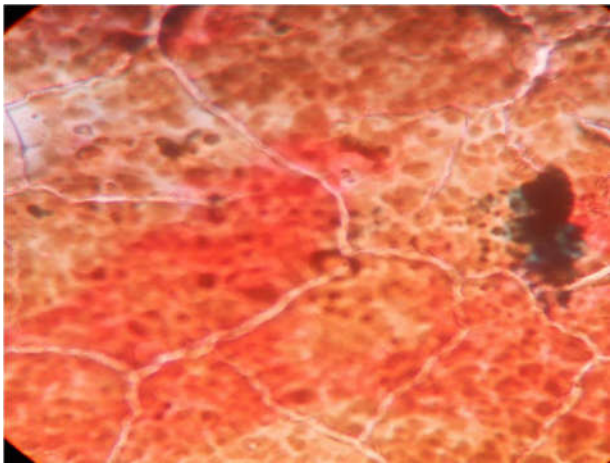

Fig. 5: Perl's stain to demonstrate iron granules

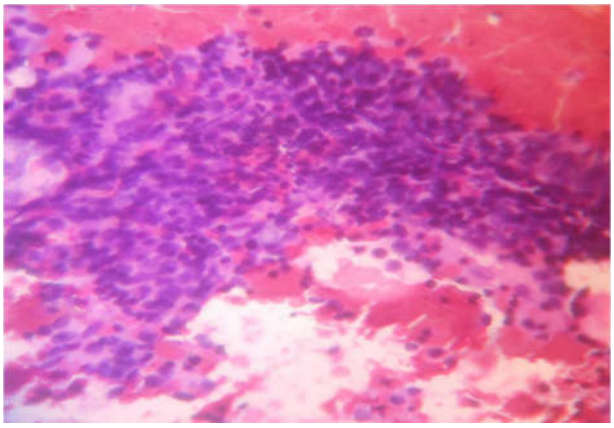

Fig. 6: Lymphoma showing monomorphous population of lymphoid cells

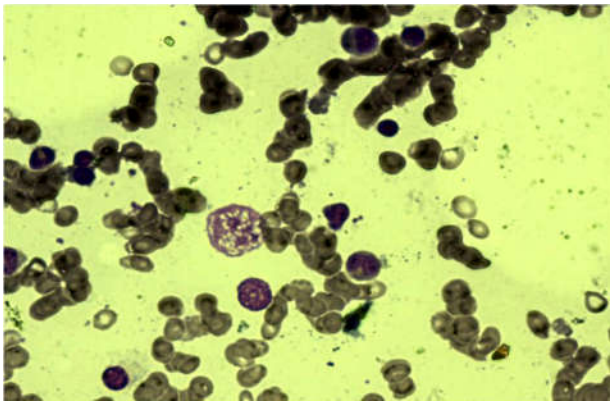

Fig. 7: Bone marrow aspiration showing foamy cells in Neimannpicks disease

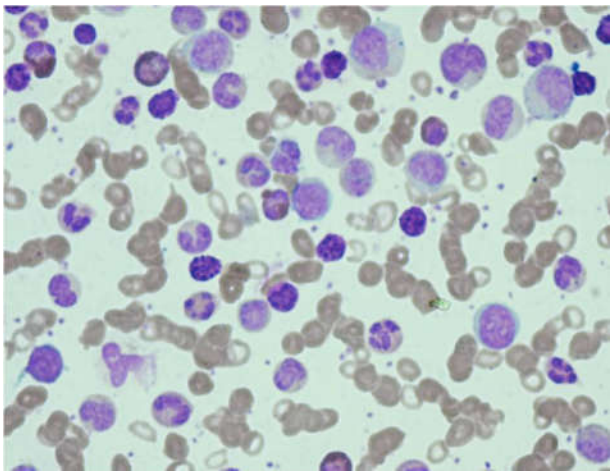

Fig. 8: Chronic myeloid leukemia seen in bicytopenia

Discussion

Pancytopenia ia a common haematological finding with variable clinical presentations. It often poses diagnostic challenge to physician and the knowledge of accurate etiologies of this condition is crucial in the management of the patient [2]. The differences in the etiology of pancytopenia are due to differences in population characteristics such as age pattern, nutritional status, socioeconomic parameters, and prevalence of infection in geographic region [3-7]. In our study megaloblastic anemia (25.39% & 13.95%) was the commonest cause of pancytopenia and bicytopenia respectively, followed by hypoplastic marrow (20.63%) and erythroid hyperplasia (20.63%) in pancytopenia and 9.30% each of erythroid hyperplasia, normocellular marrow and myelodysplastic syndrome in bicytopenia. New onset pancytopenia outside this setting, in both children and adults, can prove to be a diagnostic dilemma, and causes include congenital and acquired bone marrow failure syndromes,marrow space occupying lesions,peripheral destruction of haematopoietic cells,autoimmune disorders,infection and ineffective marrow production[8].

In our study ,megaloblastic anemia(22 cases) was the commonest cause of Pancytopenia and Bicytopenia and the commonest peripheral smear pattern was dimorphic anemia (which is in accordance with other authors) , followed by hypoplastic marrow, erythroid hyperplasia and HIV infection(13 cases each).

The causes of Pancytopenia[9] (wintrobes, vol 10th edi 1998) are due to various mechanisms like ineffective haematopoiseis with cell death in the marrow, formation of defective cells that are rapidly removed from the circulation, sequestration on destruction of cells by action of antibody, and trapping of normal cells in a hypertrophied and over active reticuloendotheilial system.

Apart from these, pancytopenia is also associated with destruction of marrow tissue by toxins, replacement by abnormal or malignant tissue, or suppression of normal marrow growth and

differentiation. In such patients bone marrow study usually provides the diagnosis. 'Bicytopenia' occurs in association with the above conditions either as a persistent finding or as pancytopenia is developing.

The study shows the nutritional anemia in developing countries like India and correction of deficiency by giving Vit B12 and folic acid therapy completely cure the hematological disorder, thereby can decrease the number of Pancytopenia and Bicytopenia.

Bone marrow aspiration showed megaloblastic Erythroid hyperplasia.Megaloblasts had the characteristic feature of sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm with cytoplasmic blebs.Giant metamyelocytes and band forms were predominant in granulocyte series [10].

HIV has been shown to cause bone marrow failure and subsequent pancytopenia. The degree of hematological findings in the course of HIV infection varies widely [8]. The study shows HIV infection is emerging as another leading cause for Pancytopenia and Bicytopenia. HIV infection was found in 13 cases of which 4 cases (30.76%) were of hypoplastic marrow followed by MDS, Erythroid hyperplasia and normal marrow 2 cases each (15.38%). Initial infection leads to lymphopenia followed by an atypical lymphocytosis which may or may not be associated with transient pancytopenia. Initially bone marrow will be hypercellular, becomes hypercellular with a resulting pancytopenia [11]. All lineages can appear dysplastic in HIV [12]. In a study conducted by Col Jyothi Kotwal et al, the bone marrow changes were predominantly normocellular marrow followed by megaloblastic change and increased plasma cells >5% [13] with the continuing rise in prevalence of HIV infection worldwide, it is important for the pathologist to recognize the hematological abnormalities and morphological changes in the bone marrow associated with HIV infection. The etiology of these findings are possibly either due to direct effects of HIV, nutritional deficiencies, opportunistic infections of marrow or the use of marrow suppressive agents [13]. Anemia in HIV patients can be a good clinical indicator to predict and assess the underlying immune status. Patients should be investigated for haematological manifestations and appropriate steps should be taken to identify and treat ther reversible factors [14].Studies have shown that certain organisms can cause bone marrow suppression,including leptospirosis and Dengue fever [15,16].

HIV was diagnosed by ELISA method as per NACO guidelines [17] in our study, bone marrow was particularly examined for cellularity, fibrosis, dysplasia and granuloma in cases of HIV infection. Thrombocytopenia cases were more in our study because of ITP and IAT(infection associated thrombocytopenia) THERE was Dengue outbreak during our study period in our area. In Infection associated thrombocytopenia (IAT), the virus might directly damage the platelets or alter them to become antigenic, resulting in specific anti platelet antibody formation. Alternatively, a virus-antivirus complex could precipitate on the platelets and damage them resulting in compensatory increase of megakaryocytes in the bone marrow [18].

12 cases (11.32%) presented with hepatomegaly and 18 cases (16.98%) presented with splenomegaly in the present study.

Commonest age group is 21–30 yrs in our study with male preponderance which is in accordance with studies done in India which show the most common age group involved to be in the third decade with male preponderance [3, 20-21].

Commonest cause of Pancytopenia and Bicytopenia was Dimorphic anemia in peripheral smear.

Clinical presentation and peripheral smear findings of rare cases like Tuberculosis, Reactive Eosinophilia, Storage Disorder and Pure Red Cell Aplasia .

Tuberculosis: 28 yrs female presented Bicytopenia (anemia and thrombocytopenia) with RA, acute GE & metabolic encephalopathy. Bone marrow aspiration and biopsy showed hypoplastic marrow with maturation arrest in myeloid component with focal areas of necrosis & Granulomatous inflammation suggestive of miliary tuberculosis.

Reactive Eosinophilia: 40 yrs female with Bicytopenia & leucocytosis, easy fatigability, acute GE & anxiety disorder. Usg shows acute cholecystitis. BMA findings were active marrow with normoblastic maturation with marked eosinophilic proliferation favouring a reactive process.

Pure red cell aplasia: 48 yrs female with Bicytopenia(macrocytic hypochromic anemia with leucopenia) with complaints of generalized weakness since 1 month, history of repeated bloo transfusion. On examination liver was palpable. Clinical diagnosis was Severe anemia in failure. Bone marrow study revealed hypercellular marrow (M:E– 8:1)with myeloid hyperplasia, markedly reduced erythropoiesis and mild dysmegakaryopoisis. Erythropoiesis was reduced with few early, intermediate and late normoblasts. Perl's stain showed markedly increased iron stores (5+).

Storage disorder: 2 cases were diagnosed, one was a 60 yrs female with diabetes and hypertension presented with pain abdomen, fever and hepatomegaly for evaluation. Peripheral smear showed normocytic hypochromic anemia with leucopenia, Retic of 0.8%, normal LFT, ESR of 30 mm/ hr. bone marrow study revealed normocellular marrow with normal marrow components, presence of few large abnormal cells with vacuolated cytoplasm and possibility of Niemann Pick's disease was suggested and further work up of seum Sphingomyelinase level and serum Glucocerebrosidase level.

Another case aged 1 yr female , clinically suspected storage disorder with global developmental delay and hepatomegaly. Peripheral smear showed microcytic hypochromic anemia with thrombocytopenia. Heamoglobin electrophoresis shows HbA-95%,HbF-20% & HbA_2-1.9%. Bone marrow study showed erythroid hyperplasia with numerous foamy histiocytes having fibrillary cytoplasm(crumpled tissue paper appearence) with pyknotic nuclei, suggesting possibility of Gauchers disease & advised further workup like glucocerebrosidase enzyme level & chitotriosidase enzyme assay.

In our study erythroid hyperplasia 17 cases(16.03%) is the third most common cause of pancytopenia. Erythroid hyperplasia was the most common cause in a study of 30 cases conducted by Graham.S. Maria et al [23]. In similar study done by Pathak et al, Erythroid hyperplasia was the second most common cause, 21 cases(20%), preceded by hypoplastic marrow. Relationship of Erythroid hyperplasia to p[ancytopenia is not certain.

The marrow is generally hypocellular in cases of pancytopenia caused by a pri production defects.cytopenias resulting from ineffective haematopoiesis, increased peripheral utilization or destruction of cells and bone marrow invasive processes are usually associated with normocellular or hypercellular marrow [24].

Sachin et al-1(0.47%), [1]

Surya babu-4(3.33%) [25]

Kishore khodke-1

Pathak et al-6(5.8%) [2]

Gayathri et al-nil

In our study we had reported 14 cases of MDS (13.20%). 2 casesa were seen in HIV patients ,5 cases in bicytopenic patients and 9 cases in pancytopenia, constituting 13.20% which is much higher compared to other studies. MDS are classified into 5 different morphological categories according to French American British (FAB) classification [26-28]. primarily a disease of adults,MDS is commonly characterized by progressive bone marrow failure,with several of the subtypes progressing to AML. The more high grade MDS categories that demonstrate extensive bone marrow failure,such as Refractory cytopenia with multilineage dysplasia, Refractory anaemia with excess blasts ,more commonly present with pancytopenia [29].

Cytogenic Abnormalities Associated with MDS.(Ref. Brunning et al [30].

The incidence of third commonest cause, hypoplastic marrow was 12% in our study which is in accordance with the study conducted by Klinger JM et al(14%). Little higher incidence was noted in a study conducted by et al .Out of 63 cases of pancytopenia AML (3.17%) and 2 cases of AML (3.17%) in our study. We also encountered 2 cases of AML, accounting for 4.65%, out of 43 cases of bicytopenia. Gayathri et al reported, 3 cases of AML and 1 case of ALL oin their study .Pathak et al reported 5 cases of ALL(4.9%) and 4 cases of AML(3.9%) in their study [2].

We encountered 2 case of NHL(3.17%) in our study.Pathk R et al also reported 2 cases of NHL in their study of 102 cases of pancytopenia. We found 3 cases of plasmacytosis,one case in pancytopenic patient and two cases in Bicytopenic patient. Pathak et al reported 2 cases of plasmacytosis in their study [2].

We reported 3 cases of multiple myeloma accounting to 3.18%. In our study all three cases were seen in bicytopenic patients, where as Gayathri et al has reported 1 case of multiple myeloma constituting 0.96% of 104 cases of pancytopenia and Khunger J M et al have reported an incidence of 1%.2 cases of multiple myeloma, whereas 1 case of Neimann-pick disease was reported by Gayathri et al [10], case of storage disorder by Surya Babu Sunkesula et al out of 120 cases of pancytopenia.

In our study we came across 1 case of disseminated tuberculosis. Sachin D Tonape et al reported 1 case of granulomatous reaction out of 210 cases and Surya Babu Sunkesula reported 03 cases of disseminated TB in their study. Kishore khodke et al reported 1 case TB out of 50 cases .we have not encountered even a single case of metastatic deposits in our study as well as myeloid hyperplasia.We found cases of HIV infection in our study constituting one of the most HIV important cause of pancytopenia.Where as Kishore Khodke et al reported 1 case of HIV infection in the year 1999.1 case of HIV infection in 2014 by Melina Desalphine et al [31], out of 50 cases ,1 case by Bhaskar

B Thakkar et al (2012) 100 cases[9].This finding is in contrast with the other studies and shows that the HIV infection is emerging as another important cause of pancytopenia because we are in tertiary care hospital attached with ART centre.

Conclusion

Bone marrow aspiration can diagnose majority cases of Pancytopenia and Bicytopenia, however bone marrow biopsy should be coupled with bone marrow aspiration for proper assessment of marrow. Major cause of Pancytopenia and Bicytopenia in our study are megaloblastic anemia followed by myelodysplastic syndrome, hypoplastic marrow and erythroid hyperplasia and HIV infection. Clinical examination along with other laboratory investigations like Vit B12 and folic acid levels, enzyme assays, serum electrophoresis, serology, immunological marker etc, with radiological findings are needed to arrive at proper diagnosis of haematological disorder in relevant cases.

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