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Bone Marrow Study is Still Gold Standard In Evaluation Of Peripheral Pancytopenia

[*1]Bora . Sreedhar , [2]Bodhireddy Sridhar Reddy , [3]B.V.Saiprasad ,
[4]N.V.Rajesh Krishna , [5]K.Divya Teja , [6]B. Anuradha
1,2& 3Associate professors , Dept.of Pathology,S.V Medical college,Tirupathi
4. Assistant professor , Dept.of Pathology,S.V Medical college,Tirupathi
5. Post Graduate , Dept.of Pathology,S.V Medical college,Tirupathi
6. Professor & HOD , Dept.of Pathology,S.V Medical college,Tirupathi
Corresponding Author : Bodhireddy Sridhar Reddy.

Email bsr999999@gmail.com

Abstract : *Pancytopenia is decrease in erythrocytes , total leucocytes and thrombocytes and it is a striking manifestation of many life threatening illness. The present study was done for a period of two years to know the incidence of age, sex and various causes of pancytopenia. Total 52 cases were studied with male prepondarence and youngest was 1 ½ year child and oldest 72 years. The commenest cause for pancytopenia was aplastic anaemia followed by megaloblastic anaemia. Whenerver the bone marrow comes as a dry tap trephine biopsy was conclusive for diagnosis.*

Keywords*: Pancytopenia , bone marrow aspiration , trephine biopsy , aplastic anaemia , megaloblastic anaemia.*

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I. Introduction

Pancytopenia, as the name impliles , is a decrease in erthythrocytes,total leucocytes and thrombocytes. Pancytopenia is a stricking feature of many serious and life threatening illness(1). The pattern of the disease leading to pancytopenia is expected to vary in different population groups with their variation in age pattern, nutritional status and prevalance of infective disorders. In india ,the cause of Pancytopenia is not well defined. These data , if available would help in planning the diagnostic and therapeutic approach in patients with Pancytopenia. In this study various causes of Pancytopenia were analyzed. Bone marrow aspiration and biopsy as diagnostic procedure is being increasingly used in recent years. The indications for bone marrow aspirations and biopsy have broadened in the investigation of peripheral Pancytopenia(2). Improvement in instrumentation as well as processing procedure has helped in proper evaluation under light microscopy (Jamshdi 1971 , Brinn 1979) .The diagnostic efficacy with bone marrow aspiration and biopsy has been consistently impressive In various causes of pancytopenia like Aplastic anemia , Megaloblastic anemia , Leukemias,Lymphomas and others (3).Bone marrow biopsy was first performed by PIANSE in 1903. Since then needle biopsy and aspiration have gained importance over open surgical procedure. With introduction of bone marrow needle by Jamshidi in 1971 4, the processing modes and improved light microscopic techniques , helped to increase diagnostic efficacy.

II. Aims & Objectives

1. T o evaluate cases diagnosed as Pancytopenia in peripheral blood smear with bone marrow aspiration and bone marrow biopsy findings.
2. To study the age and sex distribution of peripheral Pancytopenia cases.
3. To evaluate various causes of peripheral Pancytopenia
4. To compare this study with similar studies.

III. Material And Methods

The present study consists of 52 cases admitted in Sri Venkateswara Ramnarayan Ruia ,Government general hospital /Sri Venkateswara Medical college in the department of pathology for a period of 2 years for evaluation of various causes of peripheral pancytopenia.The incluison criteria in our study is hemaglobin < 9

gms/dl ; leucocytes < 4000 /cumm; platelets <100000 / cumm .Exclusion criteria the patients receiving mylotoxic drugs and immuno suppresive theraphy.

Complete clinical data were recorded including physical examintaion , complete haemotological study like complete hemogram with peripheral smear study and bone marrow study that includes both aspiration and trephine biopsy.The smears are stained with routine Romonowsky stains and special stains like reticulin was performed when ever necessary.

IV. Results

This study was conducted over a period of 2 years between May 2015 and March 2017, on a total of 52 cases, admitted in Sri Venkateswara Ramnarain Ruia, Government General Hospital , Tirupathi diagnosed as peripheral pancytopenia. Clinical and pathological aspects of these cases were evaluated in the Department of Pathology ,Sri Venkateswara Medical college,Tirupathi.The data collected was arranged in Table – 1 along with Age / sex distribution , clinical symptoms / signs , Blood counts , Bone marrow aspiration and Bone marrow Trephine biopsy Findings. Various haemotological disorders causing pancytopenia in our study were represented in tables .The commonest cause in our study was Aplastic Anemia (42.31%) the second commonest being megaloblastic anemia (21.15%).

Table 2 Distribution Of Pancytopaenic Disorders In The Present Study

Si No	Name Of The Disorder	No Of Cases Incidence	Incidence In Percentage
01	Aplastic Anaemia	22	42.31
02	Megaloblastic Anaemia	11	21.15
03	Hypersplenism	05	9.62
04	ALL	04	7.62
05	Myelodysplastic Syndrome	03	5.77
06	Recovery Phase Of BM depression	02	3.85
07	AML	02	3.85
08	NHL	01	1.92
09	Myelosclerosis	01	1.92
10	Normal Study	01	1.92
11	Total	52	100

The data collected was arranged according to various causes of pancytopenia , in relation to age distribution were tabulated in Table – 3. In the present study, the youngest case was from a 21/2 year child and the oldest 72 yr .

Table – 3 Age Distribution Of Pancytopenia Cases

S.NO	Disease	01-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total
01	Aplastic anemia	1	9	2	6	2	1	-	1	22
02	Megaloblastic anemia	1	3	5	1	1	-	-	-	11
03	Hyper splenism	-	2	2	1	-	-	-	-	05
04	Acute Lymphoblastic Luekemia	2	-	1	1	-	-	-	-	04
05	Myelo Dysplastic Syndrome	-	-	1	2	-	-	-	-	03
06	Acute Mye,oblastic Leukemia	-	-	1	-	-	-	1	-	02
07	Recovery phase of Bone Marrow Depression	1	-	1	-	-	-	-	-	02
08	Non Hodgikins Lymhoma	-	1	-	-	-	-	-	-	01
09	Myelosclerosis	-	-	-	1	-	-	-	-	01
10	Normal study	-	-	-	1	-	-	-	-	01
		05	15	13	13	03	01	01	01	52

The distribution of various condition causing pancytopenia in each sex were depicted in the table – 4 , of total 52 cases 32 were males and 20 were females.

TABLE – 4 Sex Distribution Of Pancytopaenic Disorders

SI.NO	**Name of the disorders**	**No. of cases Males**	**No.of cases Females**	**Incidence in percentage Male**	**Incidence in percentage Females**
01	Aplastic anaemia	10	12	19.23	23.08
02	Megaloblastic anemia	10	01	19.23	1.92
03	Hyper splenism	03	02	5.77	3.85
04	ALL	04	0	7.69	0.00
05	Myelodysplastic Syndrome	02	01	3.85	1.92
06	Recovery phase of BM depression	01	01	1.92	1.92
07	AML	01	01	1.92	1.92
08	NHL	0	01	0.00	1.92
09	Myelosclerosis	0	01	0.00	1.92
10	Normal Study	01	0	1.92	0.00
11	Total	32	20	61.54	38.46

Various clinical symptoms and signs related to pancytopenia observed in our study were tabulated in percentages (%) , in Table No .5 Pallor is the commonest sign observed in all cases.

TABLE -5 Clinical Features / Signs observed in pancytopenia cases in percentage (%)

S.NO	Clinical Features / Signs	No of Cases	Percentage (%)
01	Pallor	52	100
02	Fever	27	51.92
03	Bone tenderness	04	7.69
04	Bleeding tendency (ecchymosis & petechae)	19	36.53
05	Jaundice	03	5.76
06	Lymphadenopathy	02	3.84
07	Splenomegaly	15	28.84
08	Hepatomegaly	14	29.92

The four largest groups of cause of pancytopenia were Aplastic anemia, Megaloblastic anemia, Hyperslenism and Leukemia / Lymphomas . Blood counts of these four sub groups were shown in the table no.6

TABLE – 6 Haemotological Parameters In 4 Sub – Groups Of Pancytopenia

PARAMETER	**Aplastic Anaemia (Median Range)**	**Megaloblastic Anemia (Median Range)**	**Hyper splenism (Median Range)**	**Luekemia / Lymphoma (Median Range)**
Hb% g/dl	4.0 (2-6.3)	4.2 (2.8-8)	5.2 (2.4 – 7)	5.2 (3-8.5)
TLC / mm3	3,350 (1,500 – 3,900)	3,200 (2,200 – 3,800)	3,000 (1,800 – 3,800)	3,000 (2,600 – 3,800)
Platelets / mm3	65,500 (20,000 – 90,000)	80,000 (50,000-98,000)	68,000 (27,000 – 86,000)	40,000 (28,000- 80,000)

Hb : Haemoglobin : TLC : Total Leucocyte Count

Bone Marrow aspiration was attempted in all 52 patients but 8 cases were "Dry Taps".In those cases, we have taken the help of touch imprint smears of marrow core and also trephine biopsy for the final diagnosis.

V. Discussion

In our institute the incidence of pancytopenia was 5.4% . Out of 52 cases evaluated, aplastic anemia was the commonest cause (42.31%),followed by megaloblastic anemia (21.15%).It was found that complete clinical and other relevant parameters were needed in evaluating in the bone marrow aspiration smears and biopsy sections to arrive at a conclusive diagnosis. "Ideally the bone marrow biopsy should be reviewed with knowledge of clinical history , complete blood count , peripheral blood picture and bone marrow aspirate smears" (47) . Proved to be correct in present study. Evaluation of all the parameters along with the bone marrow aspiration smears is complementary to the biopsy. While bone marrow aspirate specimen are superior to biopsy for morphological details, biopsy specimens provide more reliable index of cellularity and often reveal

marrow infiltration and fibrosis that are not detected on aspiration. Thus both procedures are complementary and help in providing prompt and precise diagnosis in the setting of pancytopenia (48,49).

However , in megaloblastic anemia and hypersplenism groups ,biopsy did not provide any additional information comparative to aspiration. Frequently ,it is a combination of clues gathered from examination of several different preparations that leads to a correct diagnosis (50). In our study ,biopsy was performed at the same site as aspiration. The aspiration procedure did not affect the architecture in the biopsy. Provide an adequate sized biopsy is obtained ,aspiration can be performed immediately before biopsy without altering the interpretation of haemopoietic cellularity(51) was apt from the study. Raje JD et al(52) ., 1992 has stated that in their study of 110 cases ,bone marrow trephine biopsies are useful in differential diagnosis of cytopenias ,especially when bone marrow aspiration is hypocellular or dry tap and in the staging of lymphomas and multiple myelomas. In our study of 52 cases , 8 were dry taps ,which included aplastic anemia {4} megaloblastic anemia 1 acute lymphoblastic leukamia 1 myelodysplastic syndrome 1 and myelosclerosis 1 a definitive diagnosis was masde on trephine biopsy. The bone marrow touch preparation slides stained with Romanosky stains similar to the procedures for blood smears ,allow excellent morphologic detail and allow differential counts to be performed(53). In present study ,in three dry tap cases ,touch imprint smears were diagnosis. Aplastic anemia among 22 cases of aplastic anemia ,9 cases occurred in 2nd decade .bone marrow aspiration was a dry tap in 4 cases . history of analgesics and antibiotic intake was present in 4 cases and history of fever one month prior to the illness in 8 cases and no cause was found in rest of the 10 cases . Although all may search carefully for a possible etiological agent for pancytopenia ,no cause is found or suspected in about 50% of cases(53). Megaloblastic anemia was second most common cause of pancytopenia in our study , constituting 21.15%. Kale et al., from Mumbai in a study of 65 cases of pancytopenic patients ,detected megaloblastic amemia in 25.4% cases (54 Sen et al., from Rohantak, found megaloblastic anemia to be the commenest cause 39% in a study of 191 pancytopenic cases (55). Bone marrow aspiration was morphologically more revealing in identifying megaloblasts. Bone marrow biopsy although hypercellular was not much useful as large immature appearing cells were resembling blasts. Both folic acid and B12 deficiency will cause megaloblastic anemia , but the neurological abnormalities do not occur in folic acid deficiency as a rule (56).in our study ,none of the patients presented with neurological abnormalities. However , nerve conduction studies were not done.

5.1 Hypersplenism:

Hypersplenism results from congestive splenomegaly with widening of the splenic cords , increase in macrophages and / or connective tissue fibers . this leads to premature destruction of normal blood elements particularly in conditions like malignant lymphoma and leukemias involving diffusely the splenic parenchyma particularly in the red pulp (57). Probably the etiology for hypersplenism is either potal hypertension or acute, subacute or chronic infections .cases were followed up . splenectomy was done in one case and complete recovery of blood picture was observed .Acute lymphoblastic leukamia ALL here were 4 case acute lymphoblastic leukamia ,all occurred in young age groups and were of L2 type .Pancytopenia was the presenting feature in all the 4 cases. The most common change associated with scanty aspiration was bone marrow fibrosis and hypercellularity especially due to immature cells .It is concluded that dry tap should be never be dismissed as being due to faulty technique and always needs a bone marrow biopsy (58).Dry tap was obtained in one case in which biopsy confirmed the diagnosis. Myelodysplastic syndrome MDS : In myelodysplastic syndrome , the cells population in biopsy specimen varies according to the subtype (59).this was found true in our study, where out of three cases ,two were hypercellular both in aspiration and trephine biopsy,one was dry tap and found to be hypocellular in biopsy with marked fibrosis and numerous megakaryocytes with occasional foci of immature myeloid cells.

5.2 Acute Myeloblastic Leukemia.(AML)

One case presented in the middle aged and other one in elderly age group. Bone marrow aspiration revealed the definitive morphological blasts . Thorough bone marrow biopsy was not significantly contribute to the diagnosis , an additional finding in biopsy was focal patchy necrosis, which would have been missed in aspiration alone. Serial biopsies at frequent intervals can be of use in predicting the response to the chemotherapy and thus helpful in assessing the prognosis (60).

5.3 Recovery Phase Of Bone Marrow Depression

The reversible toxic effect takes the form of arrest of haematopoiesis when serum levels of certain drugs are sustained at above normal dosage for several days. Recovery of haematopoiesis normally takes place in a matter of days, when the administration of the drug is ceased (61). In our study, two patients presented with peripheral

pancytopenia and with vague history of drug intake, bone marrow aspiration showed areas of hypo and hypercellularity in these two cases, the reversible toxic effect of drug may be the cause.

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5.4 Non Hodgkins Lymphoma:

The pattern of marrow involvement may be diffuse, focal paratrabecular or non paratrabecular, interstitial, intrasinusoidal, intravascular and uncommonly marrow lesions of follicular lymphoma are characterised by recapitulation of the neoplastic follicles as found in the lymph node (62-69). Similarly ,in our study, marrow biopsy revealed normal marrow elements replaced by neoplastic follicles.

5.6 Myelosclerosis

Is one of the more vexing problems in bone marrow histopathology because of which , range of disorders that may cause marrow fibrosis and the usually difficulty in obtaining satisfactory aspirates for cytological studies (70).In our study , a case of myeloscleorosis was diagnosed, but the cause could not be established.

Study Comparisons: A total number of 52 cases were studied. Aspiration was diagnostic in 44(84.61%) case , as correlated with diagnosis made on trephine biopsy. In the remaining 8 cases 15.38% in which dry tap was obtained, trephine biopsy helped to establish the diagnosis. Neelam Marwaha et al (71) in their study had published that aspiration alone was sufficient in making diagnosis . In 372 (88.6%) cases aspiration correlated well with the diagnosis made on trephine sections, in the remaining 48 (11.5%) cases trephine biopsy was necessary for making a diagnosis due to incomplete information provided by aspiration or its inability to give correct diagnosis. These cases were mostly hypoplastic/ aplastic marrow, myelofibrosis and marrow involvement by metastic tumours and lymphomatous infiltration R.KUMAR et al 2001 published an original article on pancytopenia from AFMC, PUNE based on study of 166 patients with pancytopenia over aperiod of 4 years. The commonest causes were aplastic anemia , megaloblastic anemia, leukemia/lymphoma and hypersplenism.

The present study correlated well with the above study. The study comparisons are tabulated in the Table No.7

TABLE – 7 Causes Of Pancytopenia In Two Different Groups Of Studies Comparing With Present Study

Causes	No.of patients (AFMC)	No.of patients (AHRR)	No.of patients (in our study)
Aplastic anemia	27	22	22
Megaloblastic anemia	22	15	11
Hypersplenism	14	05	05
Acute leukemias	12	08	06
Lymphoma	07	03	01
Myelodysplastic syndrome	03	03	03
Marrow metastasis	02	0	0
Myelofibrosis (Myelosclerosis)	02	0	01
PNH	04	0	0
Kala – Azar	05	02	0
SLE	01	0	0
Maleria	02	03	0
Enteric fever	0	02	0
Malignant hitiocytosis	01*	0	0
Disseminated TB	01*	0	0
Recovery phase of Bone marrow depression	0	0	02
Normal study	0	0	01
Total	101	63	52

AFMC :Armed Forces medical college, AHRR: Army Hospital Research & Referral PNH: : Paraxysomal noctrunal Hemoglobinuria , SLE : Systemic lupus erythamatous TB : Tuberculoses (8) Diagnosed on Autopsy

In a study conducted by international agranulocytosis and aplastic anemia study from Israel and Europe in 1987 (72) the commonest cause was aplastic anemia 52.7%. In another study conducted by Hossain et al(73) from Bangladesh, 1992 aplastic anemia was the most common cause for pancytopenia. Vermal et al (74) conducted a study in india ,1992 where in aplastic anemia 40.6% was commonest cause. Our present study correlated well with the above studies. The study comparisons were tabulated in Table No.8. Mussarrat Niazi , Fazi-1 , Raziq from Peshawar, Pakistan presented an article based on astudy of 89 case of pancytopenias(75). Aplastic anemia 38.27% was the commonest cause followed by megaloblastic anemia 22%. The present study also correlated well with the above study. Deshwal et al Army Hospital and Referral , New Delhi (2002)

published an article on analysis of 52 cases of pancytopenia were aplastic anemia , megaloblastic anemia , leukemias and hypersplenism. In the present study also, the four major causes of pancytopenia are same as the above study.

STUDY	COUNTRY	YEAR	No. Of CASES	COMMONEST CAUSE OF PANCYTOPENIA	SECOND COMMON CAUSE
International Agranuclocytosis, Aplasticanemia	Israel & Europe	1987	319	Aplastic Anemia (52.7%)	Megaloblastic Anemia
Keisu	Israel & Europe	1990	100	Neoplastic Diseases, Radiation (32%)	Aplastic Anemia
Hossain et al	Bangladesh	1992	50	Aplastic Anemia	Megaloblastic Anemia
Vermal et al	INDIA	1992	202	Aplastic Anemia (40%)	Megaloblostic Anemia
Tilak et al	INDIA	1999	77	Megaloblastic Anemia (68%)	Aplastic Anemia
AFMC	INDIA	1994		Aplastic Anemia (26.73%)	Megaloblstic Anemia (21.78%)
AHRR	INDIA	1999	66	Aplastic Anemia (33.33%)	Megaloblstic Anemia (22.72%)
Dr. R.M.L Hospital Delhi	INDIA	2000	50	Megaloblastic Anemia (44%)	Aplastic Anemia
Khyber Medical College	Pakistan - Pareshawar	2000	89	Aplastic Anemia	Megaloblstic Anemia
Our study at Ramnarayan Ruia , Govt.Gen.Hospital ,Tirupathi	INDIA	2005	52	Aplastic Anemia (42.31%)	Megaloblstic Anemia (21.15%)

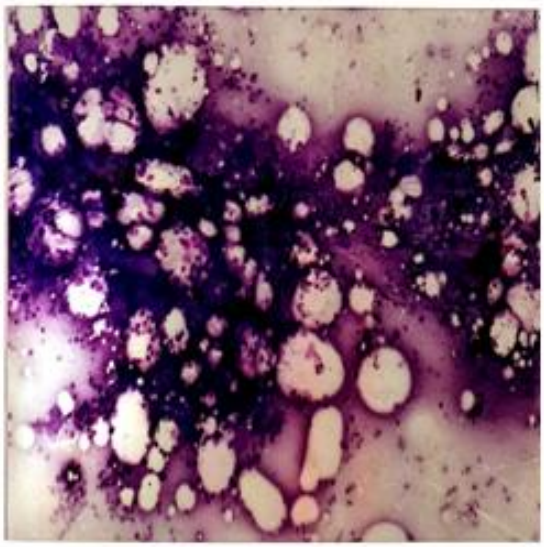
TABLE – 8 Two major causes of pancytopenia in different studies in comparison with the present study.

VI. Conclusion

The present study entitled Pancytopenia for a period of two years has been carried out to know the incidence of age,sex and various causes of pancytopenia. Both bone marrow aspiration and biopsy were carried out to know the cause of pancytopenia. The data obtained were compared with the results of similar studies from literature. The most important conclusion from the study are presented below.

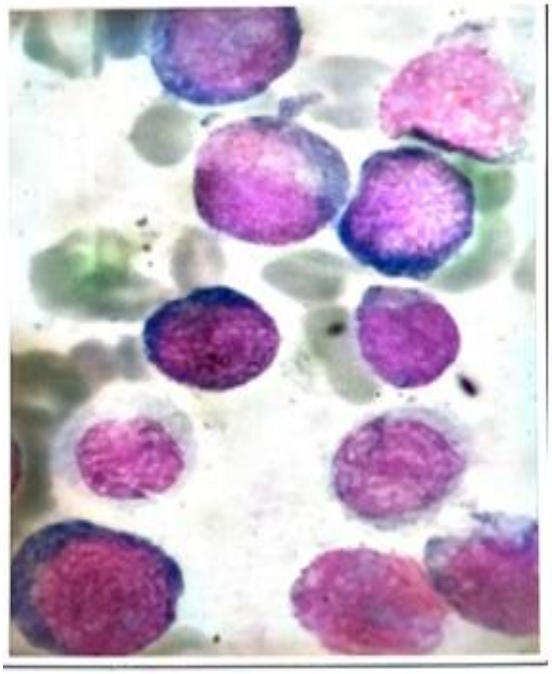
1. A total of 52 cases were studied of which 61.54% were males and 38.46% were females.
2. The youngest age was 21/2 year child and oldest from a 72 year old.
3. The commonest cause for pancytopenia was Aplastic anemia (42.31%) in the present study.
4. The second commonest casuse was Megaloblastic anemia (21.15%)
5. Other cause for pancytopenia were Hypersplenism (9.62%) Acute lymphoblastic leukemia (7.62%) Myelodyplastic syndrome (5.77%) Acute myeloblastic luekemia (3.85%) Recovery phase of bone marrow depression (3.85%) Non Hodgkins lymphoma (1.92%) Myelosclerosis(1.92%).
6. Bone marrow aspiration was Dry tap in 15.38% Trephine biopsy was conclusive for diagnosis.
7. The cause of pancytopenia in this study are correlating with similar studies conducted by others.

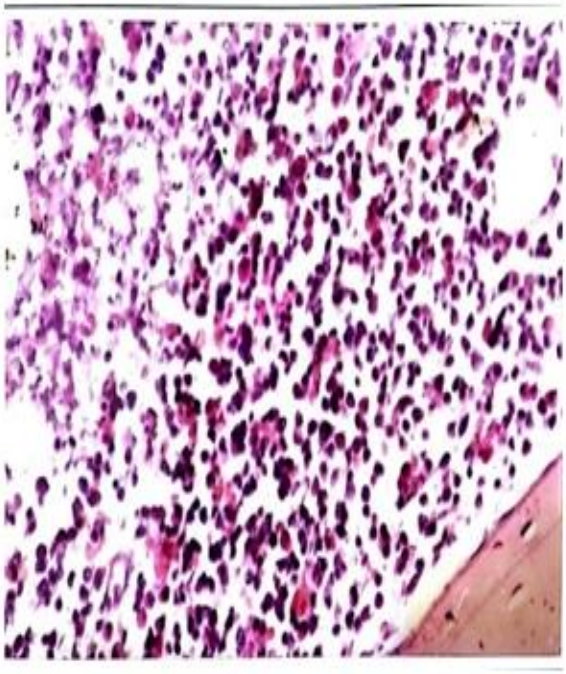
Figure no.1 **Figure no.2**



Bone Marrow Aspiration – Aplastic Anemia 10 X.
Figure no.3

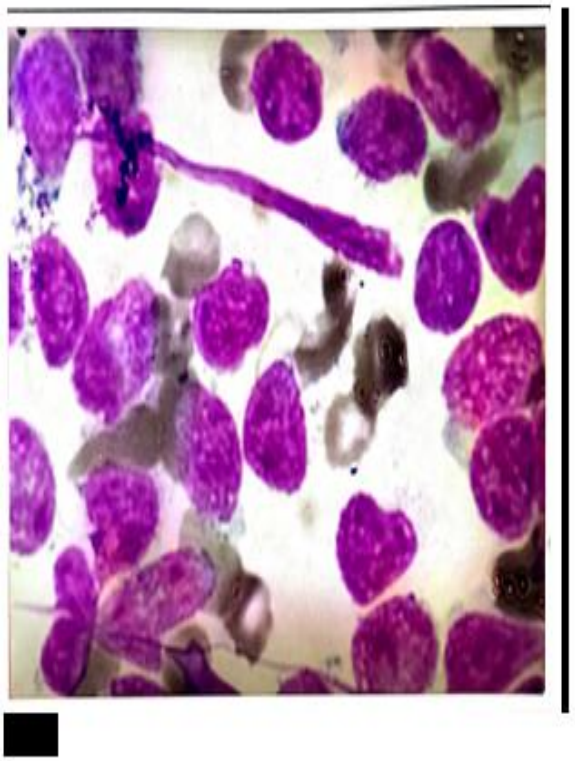
Bone Marrow Biopsy – Aplastic Anemia 10x
Figure no.4



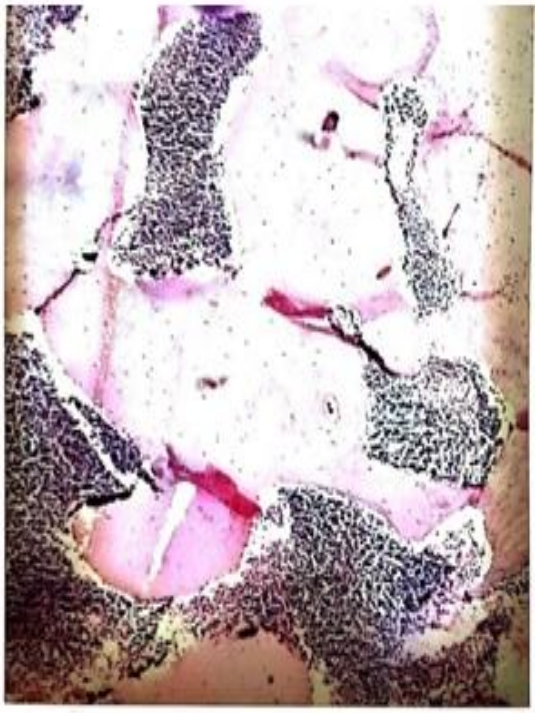


Bone Marrow Aspiration-Megaloblastic Anaemia 100x ,Bone Marrow Biosy Megalobalstic Anaemia 40

Figure no.5 **Figure no.6**

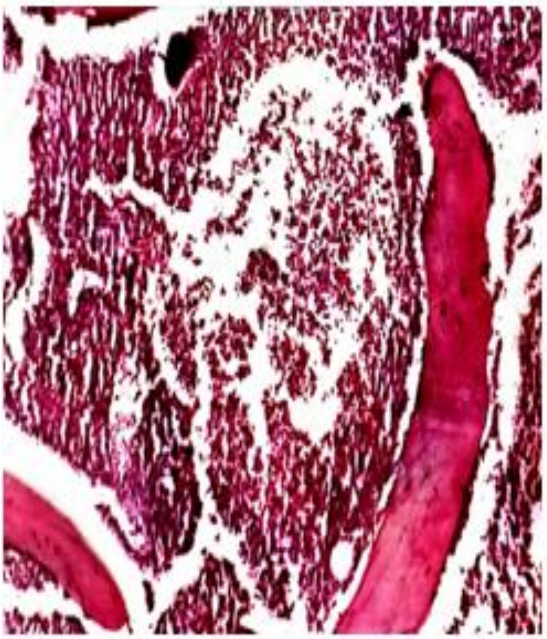


Bone Marrow Aspiration – ALL 100x



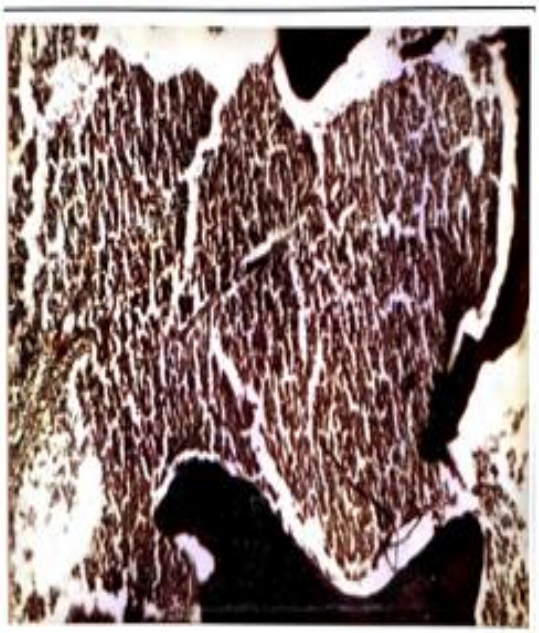
Bone Marrow Biopsy – ALL40 X

Figure no.6



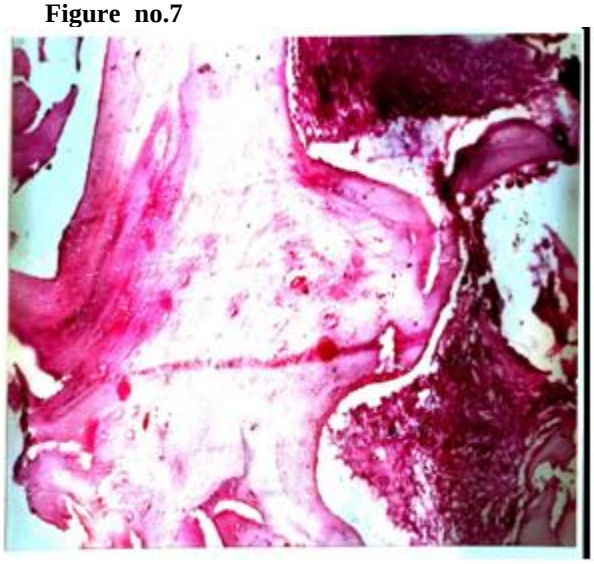
Bone Marrow Biopsy –NHL 10x, Increased

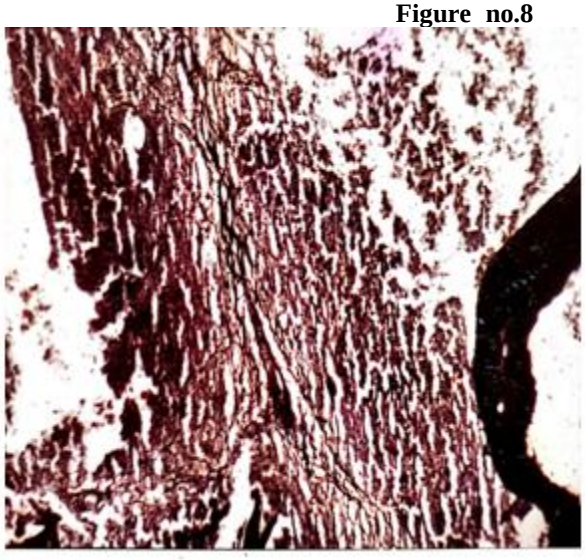
Figure no.7



Reticulinstain Showing Follicules And Reticuline Fibres

Figure no.7 **Figure no.8**





bone marrow biopsy – myelosclerosis 10x, reticulin stain

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