DIAGNOSIS OF PRIMARY MYELOFIBROSIS PRE-FIBROTIC PHASE (A Rare case report)

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INTRODUCTION

- Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm (MPN) characterized by a proliferation of prodominently megakaryocytes and granulocytes in the bone marrow that in fully developed disease is associated with reactive deposition of fibrous connective tissue and with extramedullary haematopoiesis(EMF)[(1)]. There is a stepwise evolution from an initial pre-fibrotic phase charecterised by a hypercellular marrow with absent or minimal reticulin fibrosis to a fibrotic phase with marked reticulin collagen fibrosis in the marrowand often sclerosis.

- The synonyms for PMF include- Chronic idiopathic myelofirbosis (CIMF); Agnogenic myeloid metaplasia (AMM); Myelofibrosis /sclerosis with myeloid metaplasia (MMM); Idiopathic myelofibrosis; Myeloid megakaryocytic granulocytic metaplasia (MMGM); and many others[(2)].
- Literature search revealed three study groups comprising of 1247 cases of pre-fibrotic phase of primay myelobrosis [(3,4,5)]. We could not find any single case reports. We report here the peripheral smear findings,bone marrow examination findings, cytogenetic abnormality in a case of prefibrotic phase of primary myelofibrosis in a 70 year old male patient, who presented with pain abdomen.

CASE REPORT

- A 70-year-old male complained of pain abdomen since 7 days and fullness in left flank region since 1 week. There was no history of vomiting, loose stools, fever or micturation disturbances.
- On general examination, the patient was conscious, oriented with stable vitals. His chest, cardiovascular, central nervous system examination was within normal limits. Per abdomen examination showed soft, tender, enlarged spleen 8 cms below the costal margin. No free fluid was present in the abdominal cavity.

INVESTIGATIONS

- Abdominal ultrasonography showed enlarged spleen and mild hepatomegaly. His chest X-ray was normal, liver function test, serum proteins, lipid profile, iron profile, serum B12 and folic acid were all with in normal limits, and lactic dehydrogenase (LDH) was markedly elevated. Hemogram showed normocytic,

hypochromic blood picture with neutrophilic leukocytosis (Total leukocytes count (TLC- 25,000 cells/mm^3)and polymorphs- 85%) with mild shift to left showing occational myelocytes,metamyelocytes and promyelocytes and thrombocytosis (platelet count 7.02 lakhs/mm^3). Occational late normoblasts were seen. There was no basophilia or eosinophilia. Occasional tear drop cells all were seen (Fig.1). His neutrophil alkaline phosphatase(NAP) score was 155 (control: 35-100). Thus impression of neutrophilia with thrombocytosis was given and the patient was asked to be on hematological follow-up.

- Hematological follow-up showed persistant neutrophilic leukocytosis and thrombocytosis (Fig.2). Bone marrow aspiration was done and was hypercellular for his age. Aspirate showed increase in numbers of neutrophils and atypical meyakaryocytes (Fig.3-5). Erythroid series of cells showed normal maturation. Myeloid series of cells were seen in different stages of maturation with no increase in myeloblasts. Megakaryocytes were increased in number, seen in clusters at places (Fig.6-12). Some of them showed features of dysmegakaryopoesis like, some were enlarged and some were small in size and showed deviation in nuclear/cytoplasmic ratio, abnormal pattern of chromatin clumping,associated with plump,cloud-like or balloon-shaped lobulations and frequent nacked megakaryocytic nuclei (Fig.13-21). No granuloma or hemoparasites were seen. Reticulin stain showed normal to slightly increase reticulin fibres (Fig. 22-23). Bone marrow biopsy also revealed the similar findings.

- In view of above clinical features hemogram, high NAP score and bone marrow examination features, a possibility of myeloproliferative neoplasm (MPN) was suggested. Molecular genetic analysis for JAK2 mutation was found positive for V6I7F mutation in exon 14 in JAK2 gene.
- A final diagnosis of JAK2-positive pre-fibrotic phase of primary myelofibrosis was given. All the secondary causes of myelofibrosis were ruled out.
- Patient responded to the conventional therapy of hydrea and anagrelide as there was more than 50% reduction in TLC's and thromocytes within a span of 2 months and he is still under follow-up.

DISCUSSION

- Primary myelofibrosis (PMF) a clonal myeloproliferative neoplasm (MPN) shows stepwise evolution from an initial pre-fibrotic phase to fibrotic phase. This fibrotic stage PMF is charecterised by Leukoerythroblastosis in the blood with tear drop shaped blood cells and by hepatomegaly and splenomegaly. The overt fibrotic phase is estimated to occur at 0.5-1.5 per 100000 persons per year. No registry based prevalence figures are available for the incidence of pre-fibrotic phase of PMF, but sources derived from various reference centers reveal that 30-40% of patients are first detected in the prodromal pre-fibrotic phase without significant increase in reticulin and/or collagen fibres. It occurs most commonly in the sixth and seventh decade of life and both sexes are nearly equally affected. Children are rarely affected.[1] our patient is 70-years-old.

- Exposure to benzene or ionising radiation has been documented as etiological agents in some cases. Rare familial cases of BM fibrosis in young children have been reported. None of these are noted in our case.
- Sites of involvement include blood and bone marrow. EMH (extra medullary hematopoiesis) becomes prominent in spleen in later stages and can also be seen in other sites such as liver, lymphnodes, kidney adrenal gland, duramater, gastro-intestinal tract, lung and pleura, breast, skin and soft tissue. Our case showed EMH in spleen.
- Up to 30% of patients are asymptomatic at the time of diagnosis and are discovered by detection of splenomegaly during a routine physical examination or when a routine blood count discloses anemia, leukocytosis and/or thrombocytosis. Less commonly, the diagnosis results from discovery of unexplained leukoerythroblastosis or an increased lactic dehydrogenase (LDH). In the initial pre-fibrotic phase of PMF, the only finding may be marked thrombocytosis mimicking Essential thrombocythemia (ET). Therefore a sustained thrombocytosis cannot by itself discriminate between pre-fibrotic PMF and ET. Constitutional symptoms may include fatigue, dyspnoea, weight loss, night sweats, low-grade fever and bleeding episodes. Gouty arthritis and renal stones due to hyper-uricaemia may also occur. Splenomegaly of varying degree is detected in upto 90% of patients and may be massive, nearly 50% have hepatomegaly.[6] Our patient presented with pain abdomen and spleenomegaly.

- The classical picture of advanced PMF includes PB smear that shows leukoeryerythroblastosis and anisopoikilocytosis (particularly tear droped cells) associated with hypocellular BM with marked reticulin and collagen fibrosis and organomegaly caused by EMH. However morphological and clinical findings vary considerably at diagnosis depending on whether the patient is first encountered during pre-fibrotic or fibrotic phase of the disease.
- In the pre-fibrotic phase of PMF peripheral blood shows mild normocytic anaemia with poikilocytosis including occasional tear dropcells, nucleated RBCs, thombocytosis and mild to moderate leukocytosis ($25x10^9$/lit) with some immature forms [2,8]. The marrow is hypercellular with an increase in number of neutrophils and atypical megakaryocytes. There may be a mild shift to left in granulopoiesis, but usually metamyelocytes, bands and segment form predominate. Myeloblasts are not increased in percentage and conspicuous clusters of blasts are not observed. In most cases eythropoiesis is reduced in quantity but early erythroid precussors are prominent in some patients. The megakaryocytes are markedly abnormal and their histotopography and morphology is the key to the recognition of pre-fibrotic phase of PMF. The megakaryocytes often form dense clusters of variable size that are frequently adjacent to BM vascular sinuses and the bone trabeculae. Most megakaryocytes are enlarged but small megakaryocytes may also be seen which can be detected by immunohistochemistry. Deviations from the normal nuclear : cytoplasmic ratio (an expression of defective maturation), abnormal pattern of chromatin clumping with

bulbous “cloud-like” or "balloon-shaped” nuclei and the frequent occurence of bare megakaryocytic nuclei are all typical findings. Similar findings were seen in our case. Overall in PMF the megakaryocytes are more atypical than in any other type of MPN. Careful BM morphological examination is particularly crucial in distinguishing pre-fibrotic PMF with accompanying thrombocytosis from essential thrombocythaemia (ET) as severe dysmorphia is not seen in ET. Reticulin fibrosis is minimal or even absent , during this stage, if present it is usually focal and tends to be concentrated around the vessels as in our case. The majority of cases with pre-fibrotic and early (reticulin) fibrotic phases of PMF eventually transform to overt fibrotic/sclerotic myelofirbosis associated with EMH[(1)].

- No genetic defect specific for PMF has been identified. Approximately 50% of patients with PMF exhibit the JAK2V617F mutation and its incidence in pre-fibrotic phase has not been well studied. This mutation was seen in our case. Although the presence of mutation confirms the clonality of the proliferation, it is also found in PV and ET and thus does not distinguish PMF from these MPN, but helps in distinguishing from reactive condition that lead to BM fibrosis.

CONCLUSION

Carefull analysis of clinical features, Peripheral smear , BM and cytogenic abnormality findings help in the diagnosis of PMF in pre or early fibrotic phase which in turn helps to increase the median of survival time from approximately 3 to 7 years in patients diagnosed in fibrotic phase to 10 to 15 years in patients diagnosed on early pre-fibrotic phase and hence help to improve the prognosis in these patients.

REFERENCES

1. Thele J, Kvasnicka HM, Tefferi A, Barosi G, Orazi A, vardiman JW. Primary myelofibrosis.In: Swerdlow SH, Campo E , Harris NL, Jaffe ES, Pileri SA, Stein H, et al, editiors. World Health organisation classification of tumours of Haematopoietic and lymphoid tissues. Lyon: IARC Press; 2008. p44-7.
2. Robert E, Hutichison, Naif Z, Abraham Jr. Leukocytic disorders. In: Mcpherson RA, Pincuss MR, edito rs. Henry's Clinical Diagnosis and Management by Laboratory Methods. 21st ed. Philadelphia: Saunders ;2007; p 561-62.
3. Thiele J, Kvasnicka HM, Boeltken B, Zankovich R, Diehl V, Fischer R. Initial (prefirbrotic) stages of idiopathic (primary) myelofirbosis(IMF) – a clinicopathological study. Leukemia 1999; 13:p1741-1748.
4. Thele J. Kvasnicka HM, Mullaurer L, Buxhofer-Ausch V, Gisslinger B, Gisslinger H. Essential thrombocythaemia versus early primary myelofibrosis: a multi-center study to validate the WHO classification.blood:prepublished online March 29,2011; doi: 10-1182/blood-2010-07. 293761.
5. Gianelli U, Vener C, Bossi A, Cortinovis I, Iurlo A, Fracchiolla NS, et al. The European consensus on grading of bone marrow fibrosis allows better prognostication of patients with primary myelofibrosis. Modern pathology 2012; 25:p1193-1202.
6. Barosi G. Haffman R, Idiopathic Myelofibrosis. Semin Hematol 2005; 42: p248-258.

7. Tefferi A, Lesho TL, Schwager SM, Steensma DP, Mesa RA, Li_cy et al. The JAK2V617F tyrosine Kinase mutation in myelofibrosis with myeloid metaplasia, Lineage specificity and clinical correlates. Br J Hematol 2005;131:p320-328.
8. Lichtman MA. Idopathic myelofirbosis (Myelofibrosis with myeloid metaplasia). In Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushawky K, Prchal J, editors. Williams Hematology. 7th ed. New York: McGraw-Hill; 2006. p1295-1303.

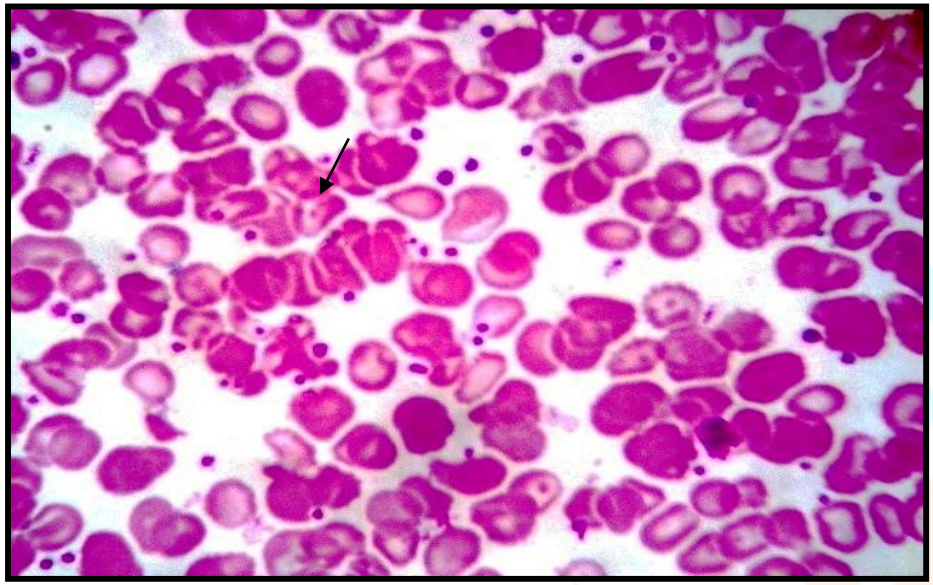


Fig 1. P.S. showing normocytic hypochromic RBCs and occational Tear drop cells (arrow)

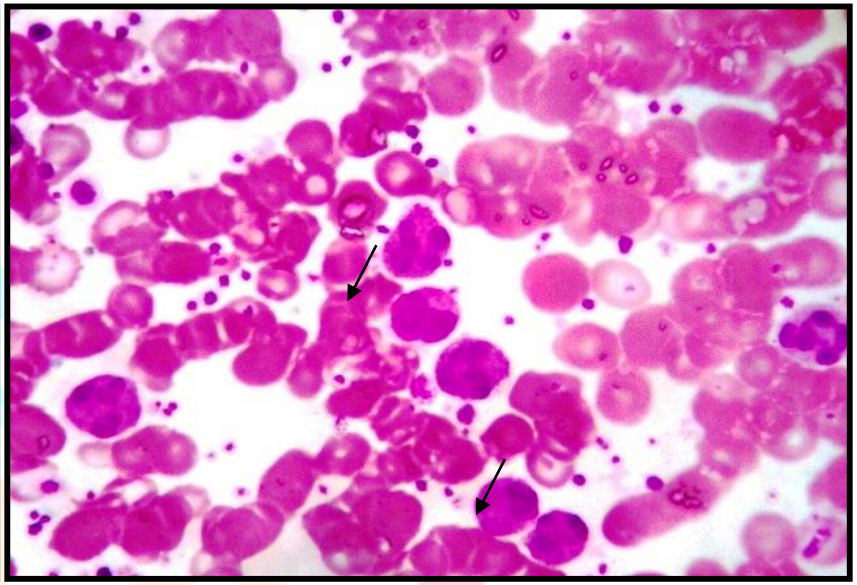
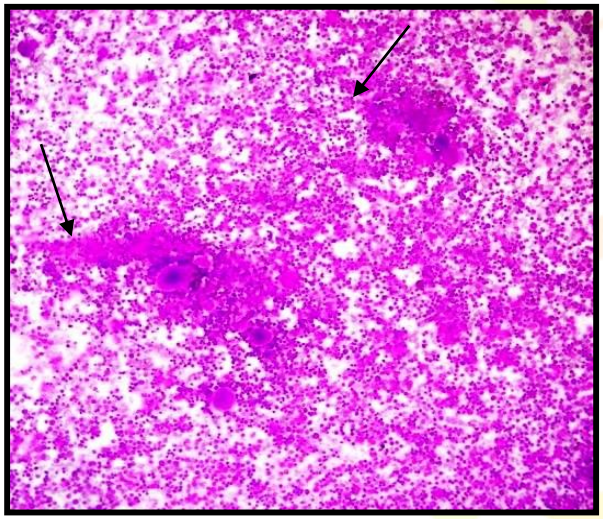
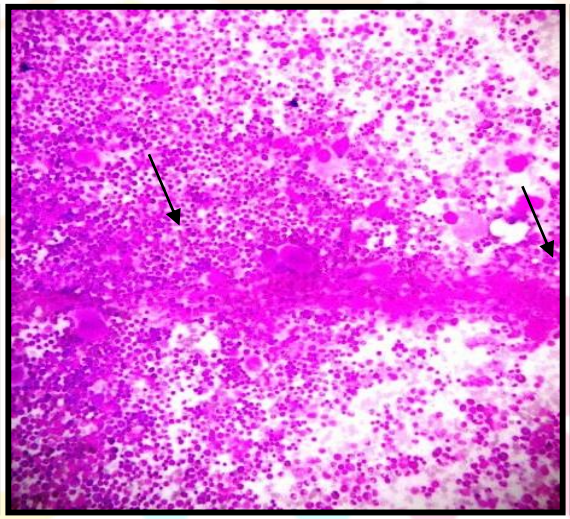


Fig 2. P.S. showing increased number of WBCs and platelets.(Leishman 1000x) (arrows)





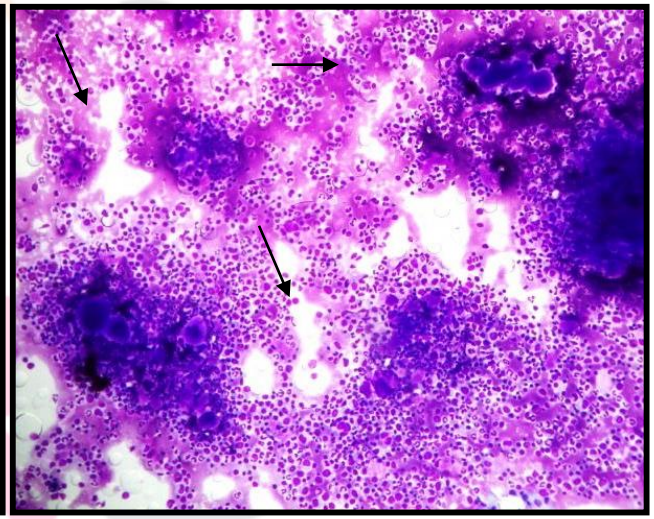


Fig. 3 Fig. 4 Fig.5

Fig3&4 Bone marrow aspiration smears showing hypercellularity and increased number of megakaryocytes (Leishman 100x) (arrows)

Fig 5.Bone marrow aspiration smears showing hypercellularity and increased number of megakaryocytes(Field's 100x) (arrows)

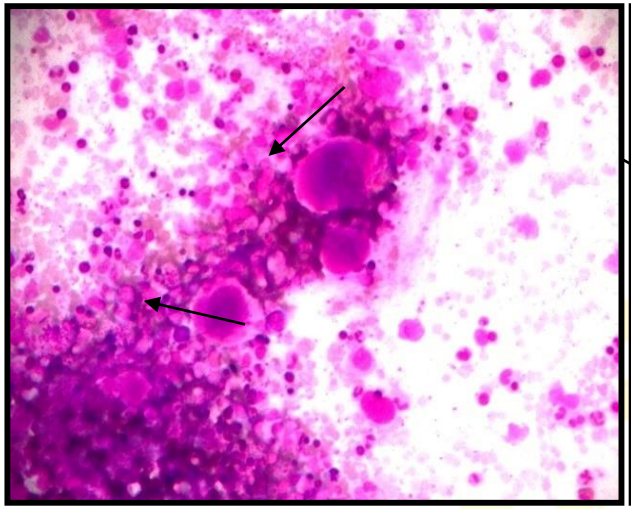


Fig. 6

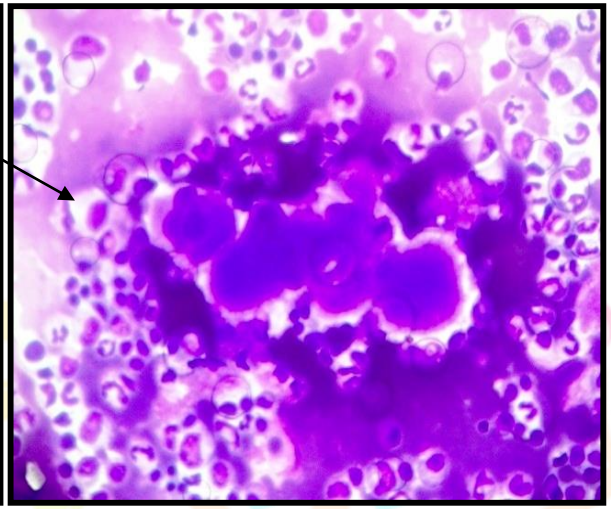


Fig. 7

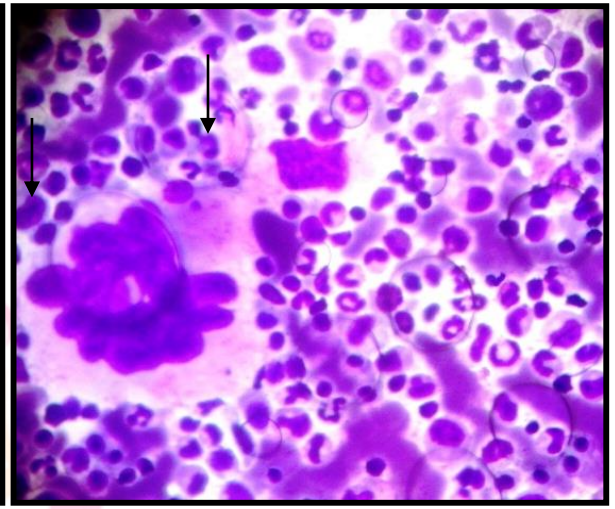


Fig. 8

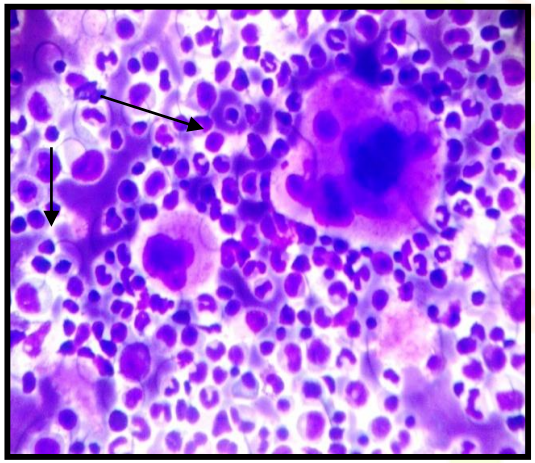


Fig. 9

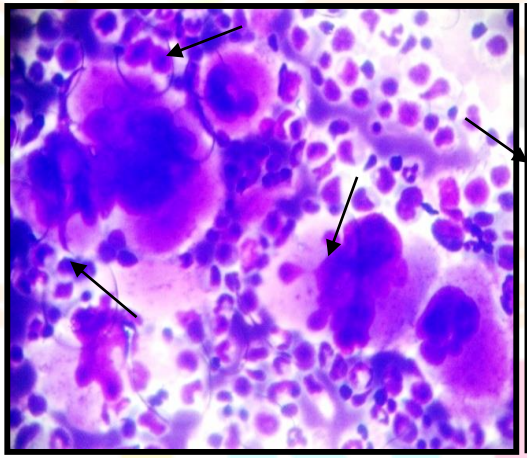


Fig. 10

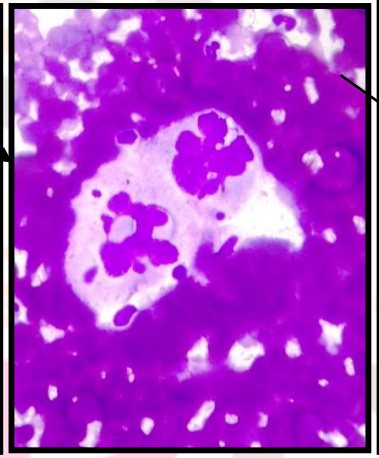


Fig. 11

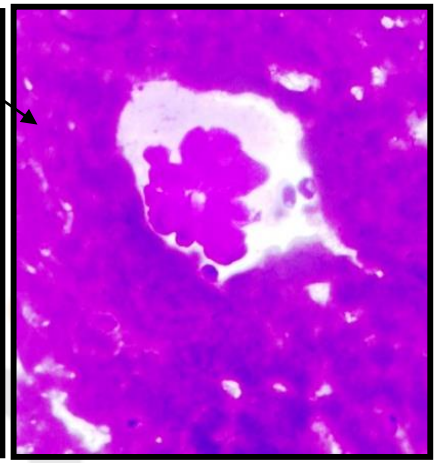


Fig. 12

Fig 6-12 Bone marrow aspiration smears showing hypercellularity and increased number of abnormal megakaryocytes (Field's 1000x) (arrows)

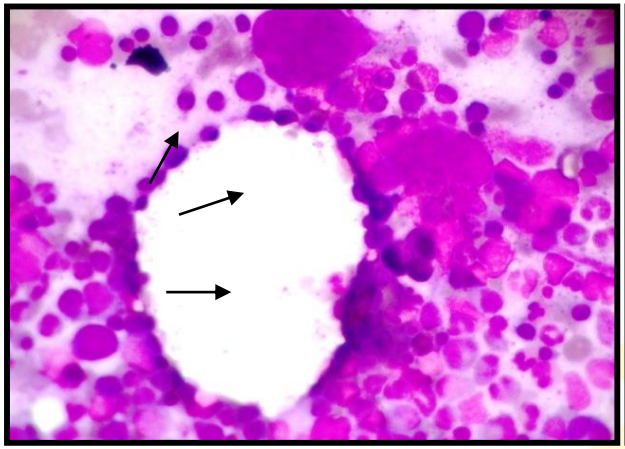


Fig.13 showing abnormal megakaryocytes around the sinusoid(Field's 100x) (arrows)

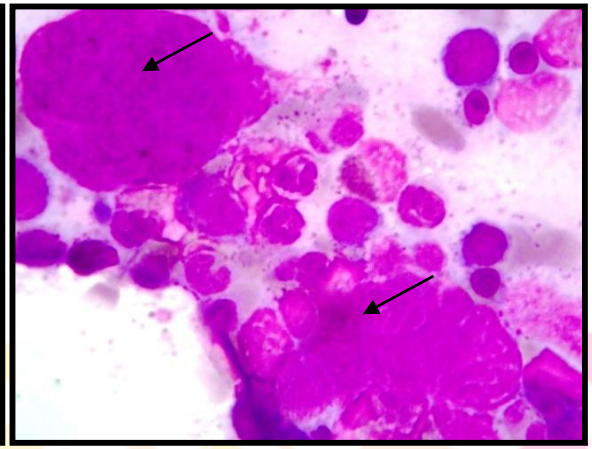


Fig. 14

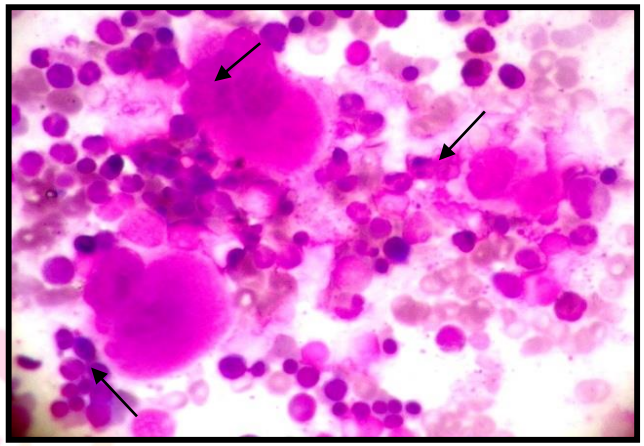


Fig. 15

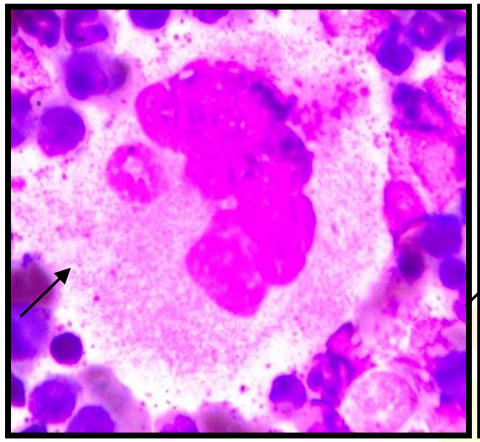


Fig. 16

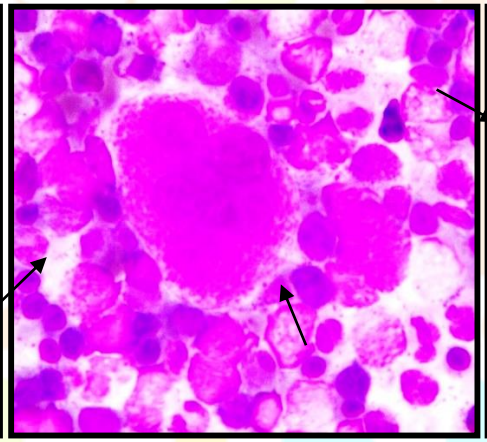


Fig.17

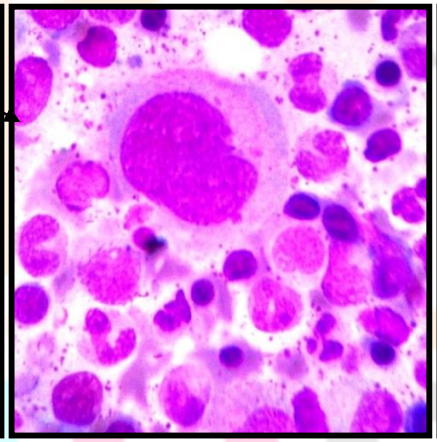


Fig.18

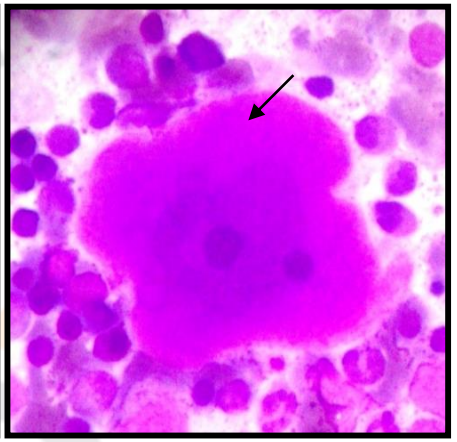


Fig.19

Fig.14-19BMA smears showing abnormal megakaryocytes (Lieshman's 1000x) (arrows)

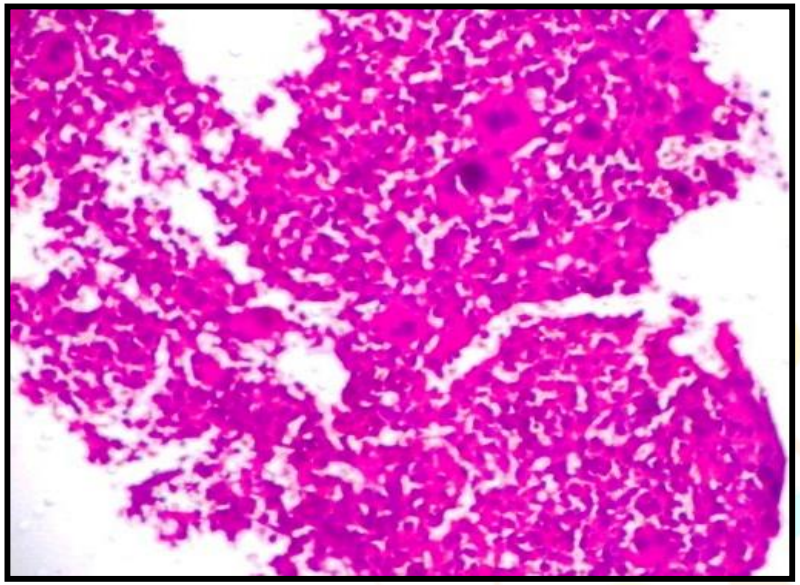


Fig 20 Bone marrow biopsy shows increased number of megakaryocytes{H & E, 100x}

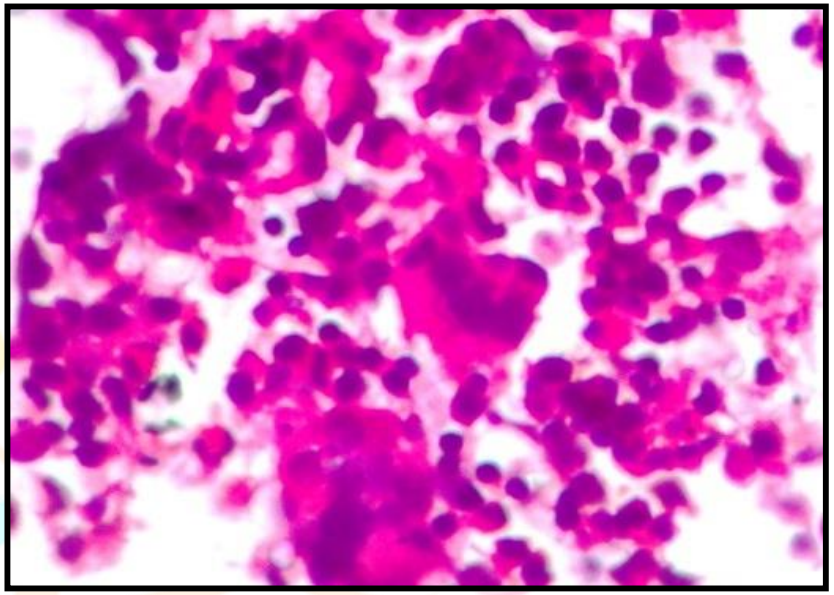


Fig 21 Bone marrow biopsy showing abnormal megakaryocytes(H&E, 450X)

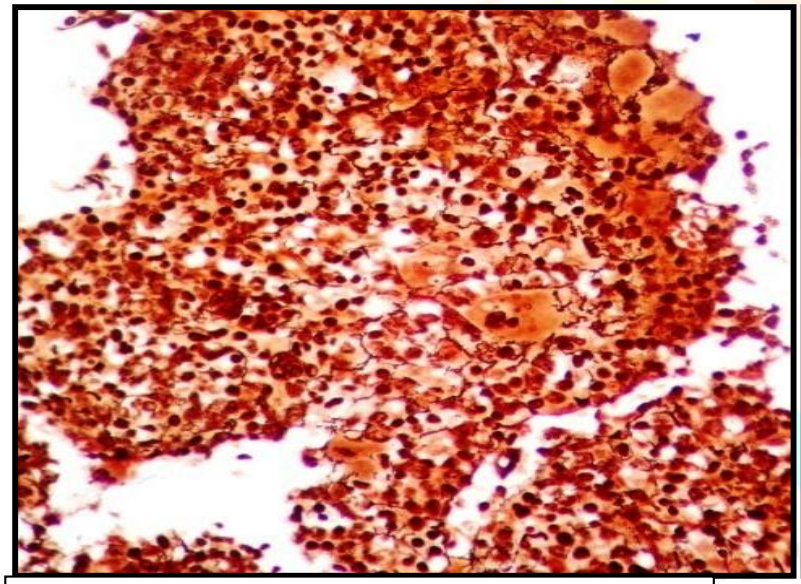


Fig 22. Bone marrow biopsy- Reticulin stain showing normal to mild increase in Reticulin fibers(100x)

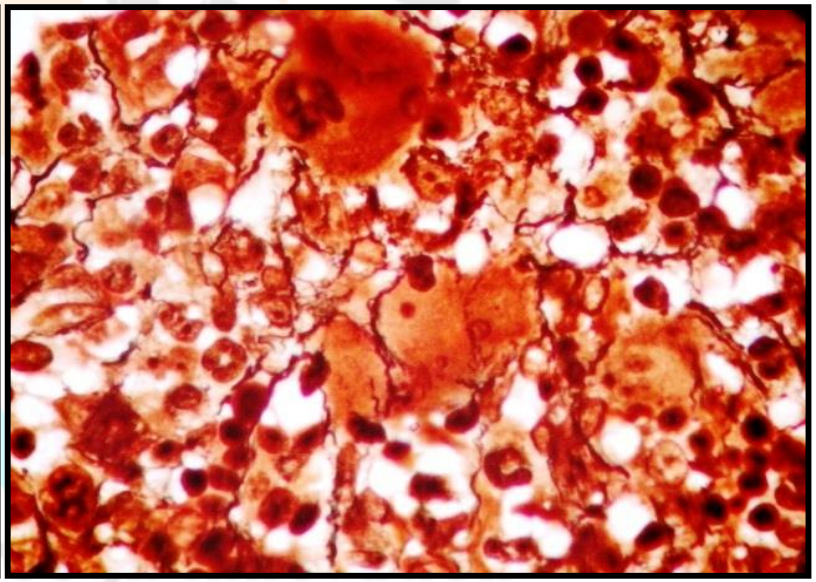


Fig.23. B M biopsy- Reticulin stain showing normal to mild increase inReticulin fibers(1000x)

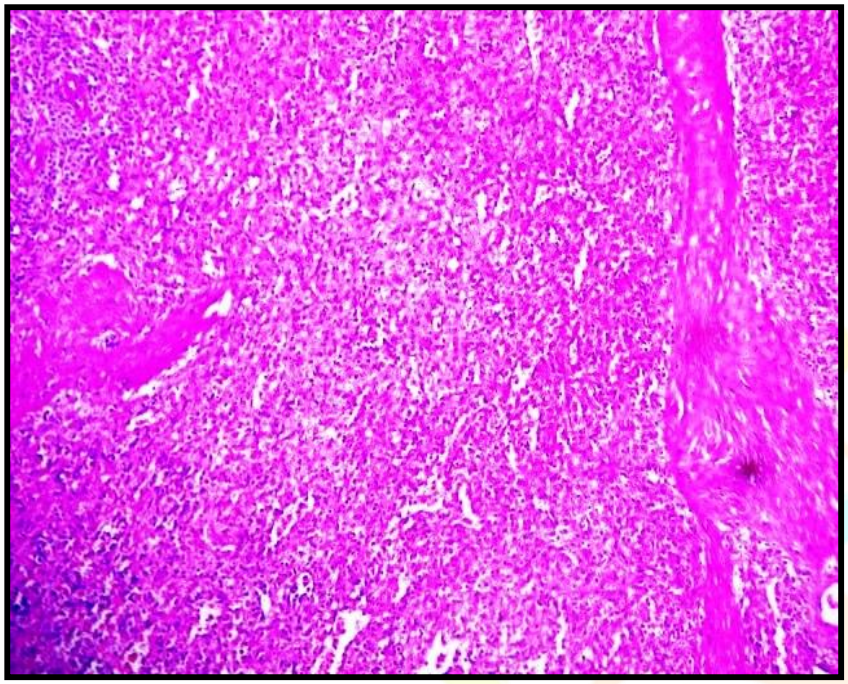


Fig.24 (H&E 100x)

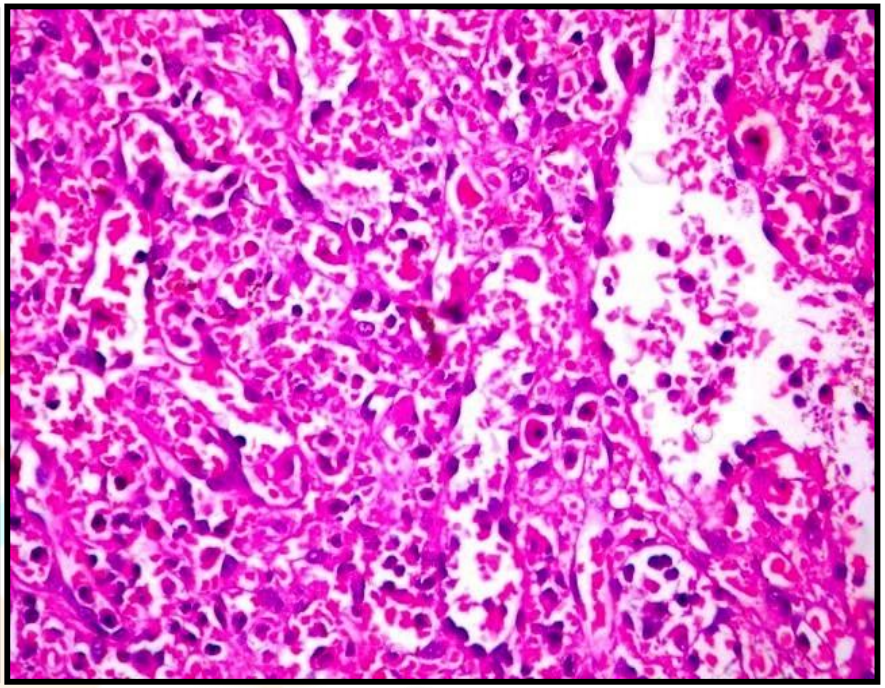


Fig 25 (H&E 450x)

Fig 24-25 HPE of spleen showing extramedullary haematopoiesis(EMH){H & E, 100X}