Original Article

Bonemarrow fibrosis condition with various underlying disorders

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Abstract

Introduction: Bone marrow fibrosis is a common morphological finding in trephine biopsies. It can be of various grades and severity in various lesions[1]. The reticulin and collagen fibers are identified by using reticulin and trichrome stains. There is a wide variety of benign and malignant disorders that are associated with bone marrow fibrosis. **Materials and Methods:** This retrospective study was done in the department of Pathology, Sri Ramachandra Medical college and Research Institute, Chennai- a tertiary care center. All bone marrow biopsies received in our department from June 2013 to May 2015 were analyzed. All cases with increased marrow fibrosis were included. Clinicopathologic analysis of patients identified with marrow fibrosis was done. Their clinical examination findings, hematological picture and histomorpholgical findings were analyzed. Reticulin and Massons trichrome stains were done to grade the fibrosis and collegenosis. **Results:** 18 patients were identified with bone marrow fibrosis in the 2 year period. The patients ranged from 14 years to 70 years of age. M:F ratio was 4:5.Among them 9 of them presented with complaints of weakness and fatiguability. They had cytopenias, and splenomegaly. The peripheral smear had leucoerythroblastic picture in 5 of these patients. They were suspected to have Primary Myelofibrosis and were advised JAK2V617F mutational analysis and BCR-ABL gene analysis.JAK2V617F was positive in 4 of them.3 of the patients were on chemotherapy. One was diagnosed with acute lymphoid leukemia, other with non hodgkins lymphoma and the other with acute myeloid leukemia. Bone marrow fibrosis was seen in a patients in autoimmune disorders including, autoimmune hemolytic anemia, pernicious anemia, and in patients with anti-nuclear antibody positivity and hypertrophic psoriasis. The H andE sections of bone marrow in 2 cases of CML were cellular having increased myelopoeisis with eosionophilia. The marrow of MDS patients had dyspoeitic features.

Keywords: Bone marrow fibrosis, Primary myelofibrosis, secondary myelofibrosis, Reticulin silver stain, Trichrome stain.

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Received Date: 10/11/2015 Revised Date: 05/12/2015 Accepted Date: 02/01/2016

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 03 January 2016

INTRODUCTION

Bone marrow fibrosis is a common morphological finding in trephine biopsies. It can be of various grades and severity in various lesions[1]. The reticulin and collagen fibers are identified by using reticulin and trichrome stains. There is a wide variety of benign and malignant disorders that are associated with bone marrow fibrosis. However histomorphology alone cannot distinguish the underlying disorders. It can be primary / idiopathic and secondary to myeloproliferative neoplasm and non-hematopoietic disorders. Fibrosis occurs relatively frequently in the evaluation of chronic myeloproliferative neoplasms. It is characterized by initially by the deposition of increased reticulin fibers. 50% of Primary myelofibrosis patients can be associated with JAK2V617F mutation.[2]

MATERIALS AND METHODS

This retrospective study was done in the department of Pathology, Sri Ramachandra Medical College and Research Institute, Chennai- A Tertiary Care Center. All bone marrow biopsies received in our department from

How to site this article: N Priyathersini *et al.* Bonemarrow fibrosis condition with various underlying disorders. *MedPulse – International Medical Journal* January 2016; 3(1): 34-38. http://www.medpulse.in (accessed 06 January 2016).

June 2013 to May 2015 were analyzed. All cases with increased marrow fibrosis were included. Clinicopathologic analysis of patients identified with marrow fibrosis was done. Their clinical examination findings, hematological picture and histomorpholgical findings were analyzed. Reticulin and Massons trichrome stains were done to grade the fibrosis and collegenosis.

RESULTS

In the two year period we received 232 bone marrow biopsies of which 18 patients were identified with bone marrow fibrosis. The patients ranged from 14 years to 70 years of age (Fig 1). M:F ratio was 4:5.(Fig 2). Among them 9 of them did not have any secondary causes of myelofibrosis, they presented with complaints of weakness and fatiguability. They had cytopenias, and splenomegaly. The peripheral smear had leucoerythroblastic picture in 5 of these patients. They were suspected to have Primary Myelofibrosis and were advised JAK2V617F mutational analysis and BCR-ABL gene analysis.JAK2V617F was positive in 4 of them 3 of the patients were on chemotherapy. One was diagnosed with acute lymphoid leukemia, other with non hodgkins lymphoma and the other with acute myeloid leukemia. Bone marrow fibrosis was seen in a patients in autoimmune disorders including, autoimmune hemolytic anemia, pernicious anemia, and in patients with anti-nuclear antibody positivity and hypertrophic psoriasis. The H and E sections of bone marrow in 2cases of CML were cellular having increased myelopoeisis with eosionophilia. The marrow of MDS patients had dyspoeitic features. The increased in reticulin fibers in these cases were identified by silver impregnation technique. The degree of fibrosis was graded by the European consensus of grading by Thiele *et al*. Masson`s Trichrome stain was done to demonstrate collagenisation. The grade of fibrosis in primary myelofibrosis patients included all 3 grades, with minimal fibrosis in cellular phase and grade 3 fibrosis in fibrotic phase. Among the CML patients one had grade 2 and the other grade 3 fibrosis. Patients with increased reticulin fibrosis and collagen deposition presented with severe cytopenias and massive splenomegaly. In other patients with minimal fibrosis, had no other findings except increased fibrosis demonstrated by reticulin silver impregnation stain.

Age distribution

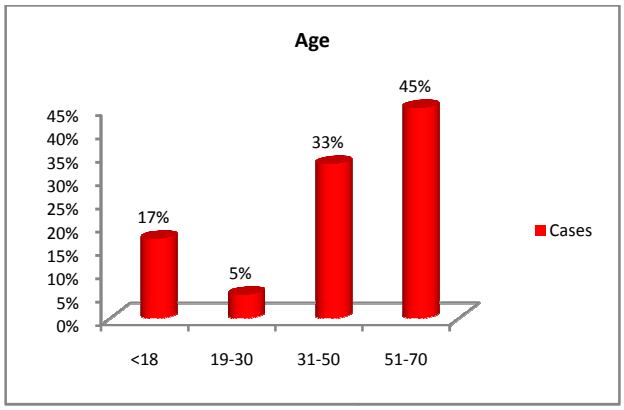

Figure 1

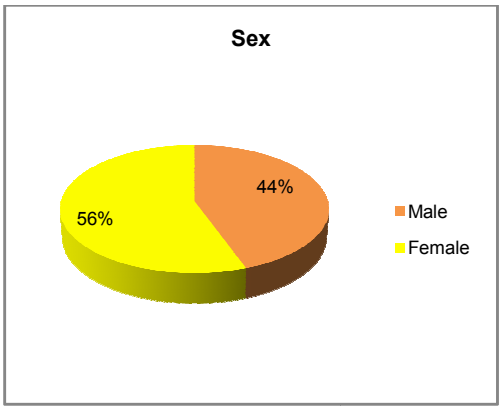

Figure 2

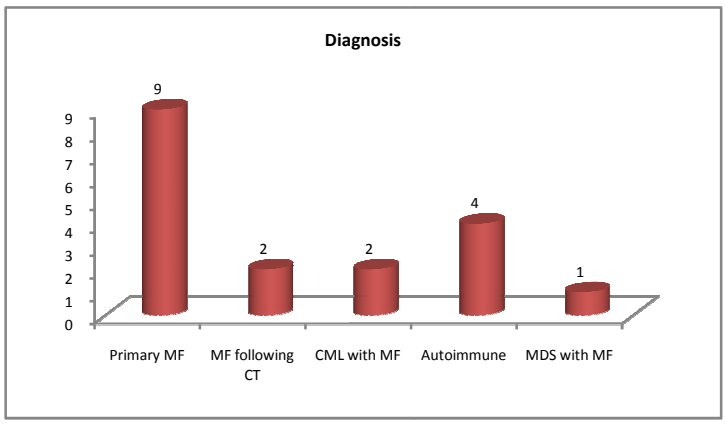

Figure 3

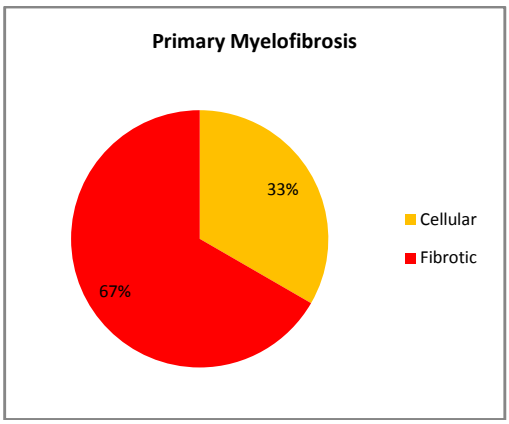

Figure 4

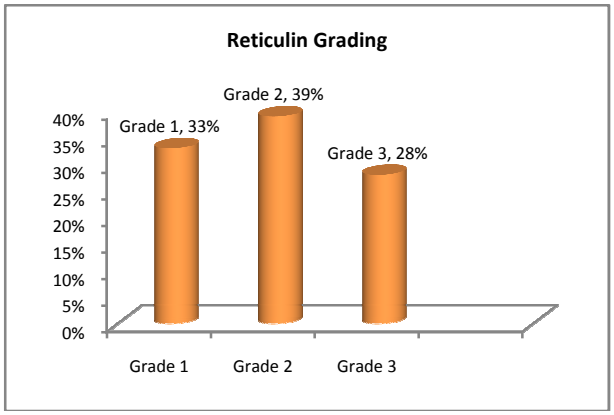

Figure 5

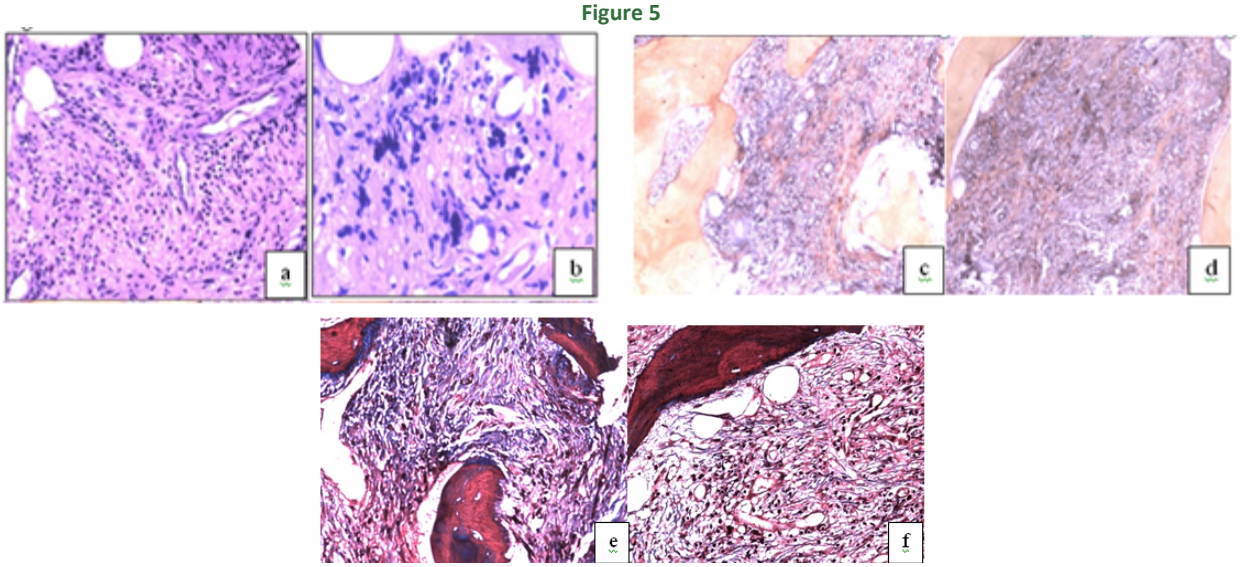

Figure 6: a) Bone marrow with fibrosis200X HandE **b)** Myelofibrosis with dyaplastic Megakaryocytes. **c,d)** Reticulin fibers increased 100xReticulin stain **e,f)** Collagenisation of Bonemarrow 200X Masson's Trichrome

DISCUSSION

Reticulin is a normal component of bone marrow. The fibers are produced by the fibroblasts in bone marrow cells. The reticulin fibers are basically small bunches of fibrils of type III collagen surrounding a core of type I collagen fibrils. The smaller fiber diameter and increased content of interfibrillar material distinguishes reticulin and collagen[3]. The routine hematoxylin and eosin sections does not always demonstrate the marrow stromal fibers. The use of special stains like the Gomori`s silverimpregmnation technique demonstrates reticulin fibers, Masson`s Trichrome trichrome stain and Van Gieson stain identifies collagen. Ideally both reticulin and trichrome stains should be done on all bone marrow biopsies[4]. Thus both reticulin and collagen fibers can be demonstrated. There are two different grading systems for fibrosis described by Bauermeister *et al* in 19715[5] and by Thiele *et al* in 2005[6](Table 1)

Table 1: Grading scales for the quantification of bone marrow reticulin and collagen (A) Quantification of bone marrow reticulin and collagen (modified Bauermeister) (Bauermeister, 1971; Bain *et al*, 2001)

0	**No reticulinfibres demonstrable**
1	Occasional fine individual fibres and foci of a fine fibre network
2	Fine fibre network throughout most of the section; no coarse fibres
3	Diffuse fibre network with scattered thick coarse fibres but no mature collagen (negative trichrome staining)
4	Diffuse, often coarse fibre network with areas of collagenization (positive trichrome staining)

Table 1 B: European consensus on the grading of bone marrow fibrosis* (Thiele *et al*, 2005)

0	Scattered linear reticulin with no intersection (cross-overs) corresponding to normal bone marrow
1	Loose network of reticulin with many intersections, especially in perivascular areas
2	Diffuse and dense increase in reticulin with extensive

	intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

*Measured per hematopoietic area (to take into account age- and disease-related cellularity.

In our study 18 patients were identified with bone marrow fibrosis in the 2 year period. All bone marrow biopsies are routinely stained with reticulin stain and if needed trichrome stain is done later. This enables to pick out unsuspected cases too. The patients ranged from 14 years to 70 years of age (Fig 1). The younger patients had underlying etiology like acute leukemia and autoimmune disorder[7,8,9,10]. Most of the elderly patients had myeloproliferative/ myelodysplastic syndrome. Primary myelofibrosis patients presented with complaints of weakness and fatigability. They had cytopenias, and splenomegaly. The peripheral smear had leucoerythroblastic picture in 5 of these patients. JAK2V617F was positive in 4 of them[11,12]. The biopsy showed a cellular marrow in three patients and 6 of them had fibrotic marrow. Chemotherapy suppresses the marrow hematopoiesis and increases the marrow fibrosis. In our study 3 of the patients were on chemotherapy. One was diagnosed with acute lymphoid leukemia, other with non hodgkins lymphoma and the other with acute myeloid leukemia. The marrow was hypoplastic with increased fibrosis. Bone marrow fibrosis was seen in a patients in autoimmune disorders including, autoimmune hemolytic anemia, pernicious anemia, and in patients with anti-nuclear antibody positivity and hypertrophic psoriasis. The H andE sections of bone marrow in 2 cases of CML were cellular having increased myelopoeisis with eosionophilia[13]. The marrow of MDS patients had dyspoeitic features. The increased in reticulin fibers in these cases were identified by silver impregnation technique. The degree of fibrosis was graded by the European consensus of grading by Thiele *et al*. Masson`s Trichrome stain was done to demonstrate collagenisation. The grade of fibrosis in primary myelofibrosis patients included all 3 grades, with minimal fibrosis in cellular phase and grade 3 fibrosis in fibrotic phase. Among the CML patients one had grade 2 and the other grade 3 fibrosis. Patients with increased reticulin fibrosis and collagen deposition presented with severe cytopenias and massive splenomegaly. In other patients with minimal fibrosis, had no other findings except increased fibrosis demonstrated by reticulin silver impregnation stain. There can be increase in bone marrow reticulin fibers in many neoplastic and non-neoplastic conditions. The increase in bone marrow fibrosis can be due to reticulin and collagen fibers. (Bain *et al*). The terminology "myelofibrosis" is used to describe the increase in marrow fibrosis in general irrespective of the underlying disorder. (Bain *et al*). However in some contexts it`s used to describe the myeloproliferative disorder Chronic Idiopathic Myelofibrosis (CIMF).(Thiele *et al*) Myelofibrosis is the second most common complication in patients with classic MPNs, which leads to cytopenias, splenomegaly, poor quality of life, and reduced survival[1]. JAK2V617F has been reported to occur in 40-91% of patients with MPN-associated myelofibrosis[1,2] The various disorders associated with grade 4 fibrosis is given blow.(Table 2). Table IV. Some causes of grade 4 bone marrow fibrosis (diffuse, often coarse reticulin fibre network with areas of collagenization) (Bain *et al*, 2001).

Generalized myelofibrosis

- Malignant disease
- Chronic idiopathic myelofibrosis* (myelofibrosis with myeloid metaplasia; also known as agnogenic myeloid metaplasia)
- Myelofibrosis secondary to essential thrombocythaemia or polycythaemiarubravera*
- Chronic myeloid leukaemia*
- Acute megakaryoblasticleukaemia*
- Other acute myeloid leukaemias
- Acute lymphoblastic leukaemia
- Systemic mastocytosis*
- Myelodysplastic syndromes (particularly secondary MDS)
- Myelofibrotic myelodysplastic syndrome (Pagliuca *et al*, 1989)
- Acute panmyelosis with myelofibrosis
- Paroxysmal nocturnal haemoglobinuria
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Plasma cell myeloma
- Metastatic tumours *
- Bone and connective tissue diseases
- Osteopetrosis
- Primary and secondary hyperparathyroidism
- Nutritional and renal rickets (vitamin D deficiency)
- Osteomalacia
- Primary hypertrophic osteoarthropathy
- Miscellaneous
- Tuberculosis
- Other granulomatous diseases
- Grey platelet syndrome
- Systemic lupus erythematosus
- Systemic sclerosis
- Sjogren syndrome
- Primary autoimmune myelofibrosis

- Antiphospholipid antibodies
- Other autoimmune myelofibrosis
- Prior thorium dioxide administration

Focal or localized

- Osteomyelitis
- Paget's disease
- Following bone marrow necrosis
- Following irradiation of the bone marrow
- Adult T-cell leukaemia/lymphoma
- Healing fracture Site of previous trephine biopsy
- *Osteosclerosis may also occur.

The exact relationship between the grade of fibrosis and the underlying disease has not been explained in most conditions. This may be due to inter-observer variation and lack of uniform fibrosis response criteria. Many studies have shown that there is very little relationship between the blood picture and the underlying fibrosis. There is partial correlation between the grade of fibrosis and disease severity in CIMF. In the early cellular phase there is little increase in reticulinfibres. The increase in fibrosis is associated with increase in megakaryocytes with atypical morphology. The prognosis is better in patients in cellular phase than fibrotic phase.

CONCLUSION

Bonemarrow fibrosis is a common histologic finding which is easy to identify, however it's difficult to point out the underlying etiology. Increased marrow fibrosis with cytopenias and massive splenomegaly is associated with primary myelofibrosis Marrow fibrosis is also seen among patients with auto immune disorders and patients on chemotherapy. Patients with myeloproliferative / myelodysplastic syndromes tend to have increased fibrosis. Hence routine staining of all bonemarrow biopsies is essential to identify the marrow fibrosis.

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Source of Support: None Declared
Conflict of Interest: None Declared