

# Hyperfibrotic myelodysplastic syndrome: a report of three cases from north India

*Hiperfibrotik miyelodisplastik sendrom: Kuzey Hindistan'dan üç olgu sunumu*

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## Abstract

Extensive fibrosis in myelodysplastic syndromes (MDS) is distinctly infrequent. Herein, we report three rare cases of hyperfibrotic MDS. This entity should be classified separately in the chronic myeloproliferative disease (CMPD)-MDS group due to variable clinical presentation and poor prognosis. (*Turk J Hematol 2009; 26: 93-6*)

**Key words:** Fibrosis, myelodysplastic syndrome, CMPD, leukemia, CMML

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## Özet

Yaygın fibrozis miyelodisplastik sendromlarda (MDS) belirgin şekilde nadir görülmektedir. Biz burada üç nadir hiperfibrotik MDS olgusunu bildiriyoruz. Bu antite, değişken klinik tablo ve kötü prognozu nedeniyle kronik miyeloproliferatif hastalıklar (KMPH)-MDS grubu içinde ayrı olarak sınıflandırılmalıdır. (*Turk J Hematol 2009; 26: 93-6*)

**Anahtar kelimeler:** Fibrozis, miyelodisplastik sendrom, KMPH, lösemi, KMML

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## Introduction

Primary bone marrow fibrosis is observed in different clonal hematological disorders including chronic myeloproliferative diseases (CMPDs) like chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelofibrosis and myeloid metaplasia, acute leukemias, especially in AML-M7, and in myelodysplastic syndromes (MDS) [1]. MDS with myelofibrosis or hyperfibrotic MDS is very uncommon and constitutes 5% of all MDS [2]. The extent of myelofibrosis in MDS varies, as mild to moderate myelofibrosis is reported in up to 50% of MDS and

marked fibrosis in 10-15% of cases [1,3-5]. Myelofibrosis may occur in any subtype of MDS, but is most common in therapy-related MDS and chronic myelomonocytic leukemia (CMML) [6]. Initially described by Sultan et al. [3], MDS with myelofibrosis is characterized by pancytopenia, minimal organomegaly, hypercellular bone marrow with marked fibrosis, trilineage dysplasia, and atypical megakaryocytic proliferation with a predominance of small forms with hypolobated nuclei [7]. On the other hand, primary myelofibrosis is characterized by splenomegaly, leukoerythroblastosis, and marrow fibrosis [8]. In general, the clinical course of hyperfibrotic MDS or MDS with

myelofibrosis is rapidly progressive with short survival, except when myelofibrosis is associated with refractory anemia (RA) or refractory anemia with ring sideroblasts (RARS) subtypes [1,3,4]. As many diseases can be associated with secondary myelofibrosis, it is important to exclude such conditions before clonal hematological disorders associated with fibrosis are considered. Since the first description of hyperfibrotic MDS, the issue of whether or not myelodysplasia with fibrosis is a distinct entity remains controversial [9]. To the best of our knowledge, hyperfibrotic MDS is very rare and reported infrequently in the literature. In this report, we describe three such cases of hyperfibrotic MDS with their differential diagnosis.

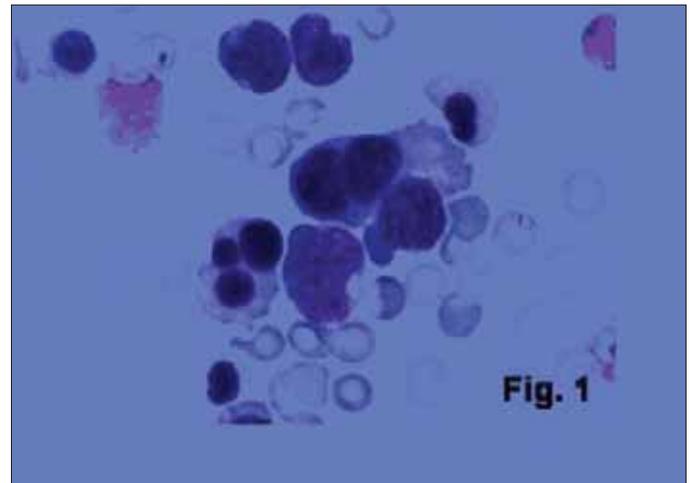
In all cases, May-Grunwald Giemsa, Prussian blue, hematoxylin-eosin, reticulin and Masson's trichrome stains were used. Cytogenetic study was not possible as in most instances aspirate resulted in dry tap. Grading of fibrosis was done according to Manoharan's grading system [10]. Iron stain was performed in all cases on bone marrow aspirate smears.

## Case Reports

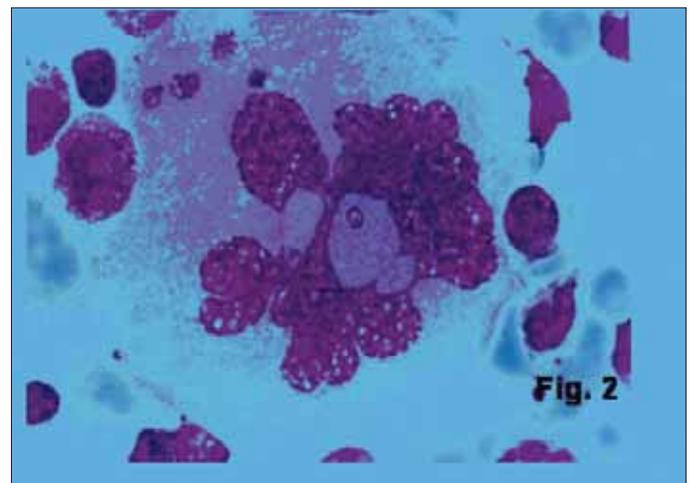
**Case 1:** SV, a three-year-old male child, presented with pallor for the past eight months. His symptoms did not proceed with fever, jaundice, weight loss or bone pain. The patient was on hematinics and received four units of blood transfusion. On examination, only the tip of the spleen was palpable and there was no hepatomegaly. Investigation revealed hemoglobin of 5.7 g/dl, mean corpuscular volume (MCV) 92 fl, total leukocyte count  $7 \times 10^9/L$ , differential count constituted blasts 11%, promyelocytes 2%, myelocytes 15%, metamyelocytes 17%, polymorphs 29%, lymphocytes 25%, and eosinophils 1%. Platelet count was  $123 \times 10^9/L$ .

Peripheral blood showed moderate macrocytosis with occasional microcytes, elliptocytes and occasional teardrop cells. No nucleated red blood cells (RBCs) were seen. Bone marrow aspirate was diluted and aparticulate. There was moderate megaloblastosis and dyserythropoiesis (Figure 1). Bone marrow aspirate smears showed increased number of megakaryocytes with enlarged and hypolobated nuclei. Eleven percent blasts were identified. Trepine biopsy was hypercellular and showed monolobated and dysplastic megakaryocytes. There was moderate reticulin fibrosis [3+]. According to existing French-American-British (FAB) classification, the case was categorized as - refractory anemia with excess blasts (RAEB) and myelofibrosis.

**Case 2:** RL, a 44-year-old male patient, presented with frequent dysentery for the past 2 years. He had received 22 units of blood transfusion up to the date of bone marrow examination and was on iron and folic acid supplement for persistent pallor. He also had 1 cm enlarged lymph node in the left axilla. His hemoglobin was 8 g/dl, total leukocyte count was  $7.6 \times 10^9/L$  and platelets were markedly reduced on smear. There were 4 to 5 nucleated RBCs/100 white blood cells (WBCs). On aspiration, bone marrow smears showed 17% blasts along with maturation arrest of granulocytic series of cells. A total of 42% myelocytes and 30% metamyelocytes were seen. The myeloid cells showed hypogranularity and megakaryocytes were increased in number and hypolobated as well as multinucleated (Figure 2). Ring sideroblasts were not seen, iron store in bone marrow was 3+ on iron stain. Bone marrow trephine biopsy showed hypercellular



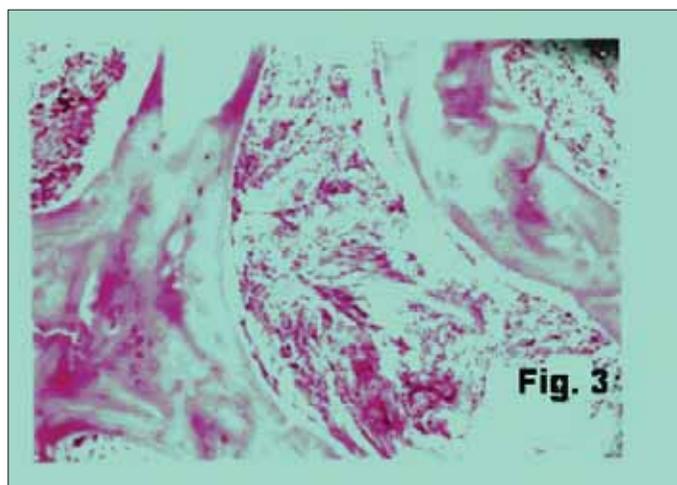
**Figure 1.** Hypercellular bone marrow aspirate with erythroid dysplasia (May-Grunwald Giemsa X200)



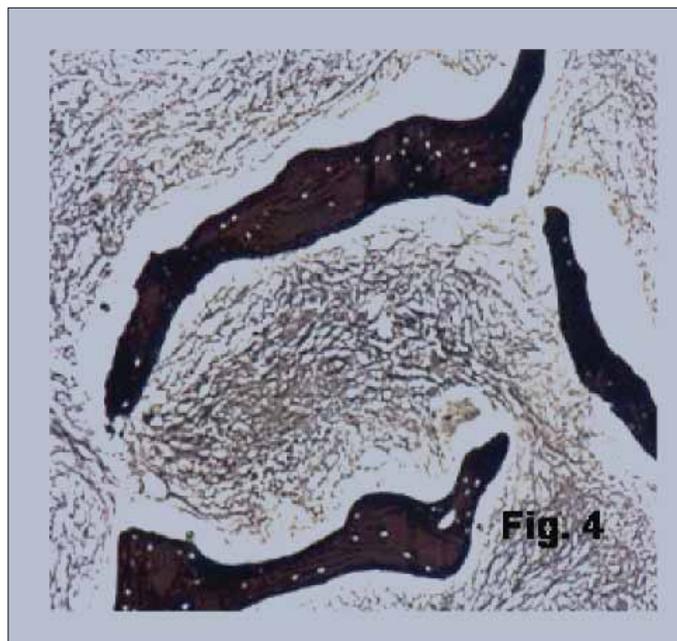
**Figure 2.** Abnormal megakaryocyte lobulation, bone marrow aspirate (May-Grunwald Giemsa X1000)

marrow spaces with marked granulocytic and megakaryocytic hyperplasia. This case also showed evidence of abnormal localization of immature granulocytic precursors [ALIP] away from bony trabeculae. The megakaryocytes were dysplastic. There was extensive marrow fibrosis with focal collagenization [4+] (Figures 3, 4). The case was reported as RAEB-2 according to FAB criteria, with myelofibrosis.

**Case 3:** RA, a 45-year-old female, presented with pyrexia of unknown origin and generalized weakness, with cough and expectoration and severe pallor for 3 months. She had received several units of blood transfusion. Though she had no hepatosplenomegaly, a few tiny lymph nodes were detected in the left submandibular and cervical area. Her hemoglobin was 8.3 g/dl, total leukocyte count  $7 \times 10^9/L$  and platelets  $37 \times 10^9/L$ . RBCs were predominantly normocytic-normochromic and platelets were reduced on smear. A few giant platelets, circulating megakaryocytes and 14 nucleated RBC/100 WBCs were noted. Bone marrow aspiration was performed twice; on the first occasion, bone marrow was particulate, normocellular and showed 3% blasts with normal maturation pattern. There were no megakaryocytes. Myeloid to erythroid ratio was 7.5:1 with normoblas-



**Figure 3.** Diffuse and coarse fibrosis (grade 3+) in bone marrow trephine biopsy (hematoxylin & eosin X200)



**Figure 4.** Diffuse and coarse reticulin fiber deposition (grade 3-4+) in bone marrow trephine biopsy (Gordon and Sweet silver impregnation X400)

tic erythropoiesis. Trephine biopsy at the same time was hypercellular and showed foci of necrosis and increased lying down of reticulin fibers [3+]. Staining for tuberculosis and other organisms was non-contributory. Bone marrow aspiration after one month was aparticle and diluted. Trephine biopsy showed hypercellular marrow spaces with diffuse coarse fibrosis [3+], which was marked around vessels. Megakaryocytes were increased in number, seen in clusters and showed moderate dysmegakaryopoiesis. This case was reported as hyperfibrotic MDS.

Follow-up was available only in Case 3, who died 6 months after performing the second marrow aspiration.

## Discussion

Hyperfibrotic MDS represents a distinct clinicopathological entity [1,11] that must be distinguished from the classical MDS

subgroups defined by the FAB Cooperative Group [12]. The incidence of myelofibrosis in primary MDS has been extensively evaluated, and ranges from 6 to 47% [11,13-16]. In another study (Kreft et al. [15], 2005), an incidence of 43% among 275 patients with Philadelphia chromosome-negative MPDs was reported. Hyperfibrotic MDS can only be well recognized by marrow biopsy, which generally shows prominent dysmegakaryopoiesis. It can be distinguished from agnogenic myeloid metaplasia by the absence of splenomegaly, teardrop RBCs and leukoerythroblastosis in peripheral blood smears, and from acute megakaryoblastic leukemia by the absence or small percentages of blasts of megakaryocytic origin [17]. Because of semantic and other diagnostic confusions related to hyperfibrotic MDS, we made a substantial effort in separating our "hyperfibrotic MDS" patients from borderline cases of primary myelofibrosis and acute leukemia with myelofibrosis. Sultan et al. [3] initially described this entity in 1981 as acute myelodysplasia with myelofibrosis. They had reported eight patients of MDS with myelofibrosis, of which four were on cytotoxic therapy and four had idiopathic MDS. However, in our cases, we excluded history of any occupational radiation or chemical exposure or recent cytotoxic therapy. Moreover, other causes of dysplasia like vitamin B12 and folate deficiency, heavy metal exposure, and human immunodeficiency virus (HIV) infection were ruled out. In the first case, a possibility of congenital dyserythropoietic anemia (CDA) was considered. CDA is a qualitative disorder of RBCs, which leads to ineffective erythropoiesis. The patient presents with anemia and features of hemolysis such as jaundice, hepatomegaly, splenomegaly and progressive iron overload. Bone marrow erythroblasts are diagnostic, as they show dyserythropoiesis, in the form of nuclear chromatin bridges. In our case, there was no jaundice or hepatosplenomegaly and dyserythropoiesis was in the form of megaloblastosis and multinucleation. Any possibility of previous systemic infection was also excluded. The onset of symptoms in hyperfibrotic MDS is usually slow, similar to other subtypes of MDS.

Takahashi et al. [18] considered MDS to be a major primary disorder for acute myelofibrosis. Patients studied in this paper were typical cases of hyperfibrotic MDS. Dysplasia observed in erythroid and granulocytic series and the associated absent organomegaly supported the diagnosis. The extent of fibrosis was variable. Major fibrosis with occasional collagen deposition was encountered in less than 10% of the cases [14]. In the present report, histopathology of bone marrow biopsy showed diffuse, dense reticulin fiber network in two patients, whereas the other (Case 2) displayed focal collagen deposits among the reticulin fibers. Hypercellularity, dysplastic erythrocytes, dysplastic megakaryocytes and ALIP (Case 2) are some of the distinguishing features by which these cases can be separated from primary myelofibrosis. Megakaryocyte hyperplasia and dysplasia, which are present in most cases with hyperfibrotic MDS, are responsible for the marrow fibrosis through release of platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF- $\beta$ ). The action of steroids in this process could justify the response of these patients to steroid therapy [1,19].

Marisavljevic et al. [20] described clinical and biological characteristics of hyperfibrotic MDS, and they found that marrow fibrosis seems to confer a poor prognosis, although survival is still related to the FAB subtype, i.e. to the blast count. There is no sex predilection for hyperfibrotic MDS [20]. Follow-up was present in only one patient (Case 3), who died within six months after diagnosis. Cases reported in the literature also showed median survivals of 6-10 months [1,18,19,21]. Biological significance of

hyperfibrotic MDS is still unclear. Some reports did not disclose whether or not hyperfibrotic subtype significantly influences the outcome of the disease [4,11,16]. On the contrary, other reports showed higher incidence of chromosomal aberrations and leukemia transformation rate, and consequently shorter survival in these cases [1,17,21].

Cytogenetic analysis could not be done in the described patients due to dry tap of bone marrow aspirates in Cases 1 and 2. In Case 3, samples for cytogenetic study were not taken as clonal hematopoietic disorder was not suspected. In general, the clinical course is rapidly progressive with short survival [1,3].

In spite of this poor prognosis, a few cases of MDS with myelofibrosis achieving a complete remission with prednisolone have been reported [19]. In addition to the percentage of blasts, which has prognostic importance, the presence of bicytopenia and pancytopenia, age, sex, and chromosomal abnormalities provide additional information that can help in predicting leukemia evolution and survival. Blast count of more than 5% was proven to be a poor prognostic factor [18]. Therefore, from the discussion, it is apparent that the diagnostic criteria for hyperfibrotic MDS should include:

- Presence of diffuse and coarse fibrosis away from blood vessels, with or without collagenization [3+ or 4+].
- The presence of morphological dysplasia in two or a series of cells.
- No organomegaly.
- Cytopenias.
- Hypercellular marrow with megakaryocytic hyperplasia.

Before making the diagnosis of hyperfibrotic MDS, one must do following:

- Acute leukemia like AML-M7 should be excluded by performing CD 61 or CD 41 immunostaining.
- Philadelphia chromosome should be studied whenever possible.
- Chronic myeloproliferative conditions should be excluded.
- Detailed history about nutritional status, occupational exposures, previous history of infections, and drug history should be taken.
- CMML should be excluded by peripheral blood findings and dual esterase staining.
- Mast cell disorders should be excluded by morphological grounds, tryptase staining or by c-kit immunostaining.

To conclude, hyperfibrotic MDS is an aggressive disorder with CMPD-MDS criteria [15,22,23]. Presently, there is no provision for this entity in the World Health Organization classification, other than in the MDS unclassifiable category [24]. Keeping in mind the diagnostic and exclusion criteria and its poor prognosis, this entity should be classified separately in the CMPD-MDS group.

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