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Clinico-Pathologic Spectrum of Myelodysplastic Syndromes

Afaq Ahmad Khan[1*], Mir Sadaqat Hassan Zaffar[2], Zeeshan Ahmad Wani[3], Sonmoon Mohapatra[4], Shyam Aggarwal[5], Tufeel Kochak[6] and Manorama Bhargava[7]

[1]Department of Hematology, JLNM Hospital, Srinagar, Jammu and Kashmir, India

[2]Department of Clinical Hematology, SKIMS, Srinagar, Jammu and Kashmir, India

[3]JLNM Hospital, Srinagar, Jammu and Kashmir, India

[4]Resident Saint Peters University Hospital, NJ.

[5]Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, India

[6]Medical Officer, NTPHC Nunner, Ganderbal, Kashmir, India

[7]Chairperson, Department of Hematology, Sir Ganga Ram Hospital, New Delhi, India

***Corresponding Author:** Afaq Ahmad Khan, Department of Hematology, JLNM Hospital, Srinagar, Jammu & Kashmir, India; Tel: 919419003346, E-mail: drafaqak@yahoo.co.in

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Abstract

Purpose: Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders with cytopenias, dyshaemopoiesis and cytogenetic abnormalities. Given the fact that the diagnosis of MDS is a challenging one and the paucicity of data on Indian patients, we studied the clinical, morphological and cytogenetic profile of 25 patients.

Method: 25 cases of the myelodysplastic syndromes diagnosed as per the WHO classification 2008 were taken and their clinical, pathological, cytogenetic profile studied. Secondary causes of dysplasia were excluded. Reasons of delay in diagnosis were assessed. Peripheral smear and bone marrow aspirate smears were stained with Wright Geimsa stain and other stains wherever applicable. Bone marrow biopsy was processed using 10% buffered formalin plus glacial acetic acid and stained with Haematoxylin and Eosin as well as appropriate histochemical stains e.g, reticulin, as per requirement. Cytogenetic study was done by conventional karyotyping or by Fluorescence *in situ* hybridization (FISH) technique. Data was analyzed by SPSS 17 for Windows statistics package (Microsoft Corp., Richmond, VA).

Results: The younger age of onset, RAEB as commoner presentation, lower yield of cytogenetics, somewhat different cytogenetic profile, possible different etiological factors, and lag in diagnosis due to decreased awareness among local practitioners, economic reasons and low educational status characterized our subset of MDS patients in this study

Conclusion: Despite the advancements in understanding the molecular biology of myelodysplastic syndrome, its diagnosis remains one of exclusion and still the cornerstone for diagnosis rests on morphological assessment of bone marrow, backed up by high index of clinical suspicion and cytogenetic analysis. This was reaffirmed in our study. Keeping in view the above findings and limited number of Indian studies on MDS, a large scale study on MDS appears to be the need of the hour.

Keywords: Dysplasia; Cytopenias; Cytogenetics

Introduction

The myelodysplastic syndromes (MDS) are a group of hematologic disorders characterized by ineffective clonal hematopoiesis and a tendency for leukemic transformation [1]. These diseases share a mono to multilineage peripheral cytopenias contrasted with normal to hyper cellularity in the bone marrow with significant dysplasia. Clinical variability of MDS, diversity of cytomorphological phenotypes and genetic heterogeneity can make the diagnosis and assignment of prognosis a challenge. Given the recent development of new treatments which can potentially change the course of the disease, it is essential to make the correct diagnosis. The diagnosis of MDS is based on clinical findings, hemogram and peripheral smear examination, bone marrow aspirate & biopsy, cytogenetics and in some cases molecular analysis.

Myelodysplastic syndromes typically affect older individuals with a median age of around 70 years and a male preponderance. The annual incidence is 3-5/100,000 persons which may rise sharply after 70 years to > 20/100000 persons [2].

The majority of the primary adult MDS patients present with features of bone marrow failure. Majority complain of fatigue due to anemia while a subset of patients present with infections or bleeding. Lymphadenopathy, hepatomegaly and splenomegaly are rarely found. Twenty percent of primary adult MDS patients are diagnosed from an incidental blood count. Occasionally MDS can be associated with rarer presentations e.g, immune mediated diseases like SLE, immune thrombocytopenia, hemolysis etc. [3]. MDS is often difficult to recognize since the symptoms can closely resemble those of other diseases. It is commonly confused with one of these diseases: aplastic anemia, leukemia, immunodeficiencies and autoimmune disorders, HIV infection, and chronic diseases (such as rheumatoid arthritis), immune thrombocytopenia and nutritional anemias. Before labeling patient as having MDS, the above masqueraders need to be ruled out by detailed clinical and investigative evaluation.

Bone marrow morphology is central to the diagnosis of MDS. Morphological examination can identify dysplasia in one or multiple cell lines with or without excess blasts. For the diagnosis of MDS, the dysplasia has to be significant i.e., ≥10% of the involved lineage. There are numerous secondary causes of dysplasia which need to be ruled out rigorously. Common among these are Vitamin B_{12} and folic acid deficiency, viral infections like HIV, Parvo virus B19, hepatitis B and C, heavy metal exposure, tuberculosis/anti-tubercular therapy (ATT) and other drugs and various rarer causes like chemo-radiation, G-CSF, paroxysmal nocturnal hemoglobinuria (PNH) and congenital dyserythropoietic anemia [4].

Due to the relative non specific nature of the morphological changes in MDS, ascertainment of clonality by cytogenetic and molecular studies have assumed a major role in the evaluation of patients with MDS. Clonal cytogenetic abnormalities are seen in approximately 50% of patients. The common cytogenetic abnormalities seen in MDS include del5q/monosomy5, del7q/monosomy7, trisomy8, del20q, -Y and complex karyotype. A few of these are associated with distinct clinico-pathologic syndromes. Some clonal cytogenetic abnormalities occurring in MDS are not definitive evidence for this disorder in the absence of morphological criteria e.g.,-Y, +8 or del20q as the sole abnormality [4]. The diagnosis of MDS can also be made based on Minimal Diagnostic Criteria as recommended by International Working Conference 2007 (Table 1).

There is a paucity of data on Indian patients with MDS, with regard to their clinical presentation and their pathological and cytogenetic profiles. The few large studies available found Indian patients to be younger at diagnosis, have a higher incidence of higher grade subtypes, showed different cytogenetic findings as compared to western literature with increased frequency in patients exposed to pesticides and other toxins. The present study was an attempt to study the clinico-pathological and cytogenetic spectrum in the Indian population. The aims and objectives were to evaluate clinical profiles of myelodysplastic syndromes and their pathological correlation in Indian patients, to study the cytogenetic findings in the above group and to assess the lag period to diagnosis and the reasons thereof in these patients.

A. Prerequisite Criteria (both 1 & 2 required)

1. Constant cytopenia in one or more of the following cell lineages: erythroid (Hemoglobin < 11g/dl); neutrophilic (absolute neutrophil count< 1.5×10^9 /L); megakaryocytic (platelets<100×10^9 /L)
2. Exclusion of all other hematopoietic or nonhematopoietic as the primary reason for cytopenia/dysplasia.

B. MDS related decisive criteria (at least one required)

1. Dysplasia in ≥10% of all cells in at least one of the following lineages in the BM smear: erythroid, neutrophilic, or megakaryocytic, or >15% ring sideroblasts(iron stain)
2. 5-19% blasts in PB or BM
3. Typical chromosomal abnormality(by conventional karyotyping or FISH)

C. Co- Criteria (for patients fulfilling A but not B criteria who otherwise show typical clinical features e.g, transfusion dependant macrocytic anemia) at least one required.

1. Abnormal phenotype of BM cells clearly indicative of monoclonal population of erythroid and/or myeloid cells, determined by flow cytometry.
2. Clear molecular signs of a monoclonal cell population on X inactivation assay, gene chip profiling or point mutation analysis(e.g, RAS mutations)
3. Markedly & persistently reduced colony formation of BM or circulating progenitor cells by colony forming assay

Note: WHO 2008 recommends hemoglobin level of <10g/dl and absolute neutrophil count of $<1.8\times10^9$/L for cytopenias.

Table 1: Minimal diagnostic criteria for MDS

Material and Methods

Study Location

This study was conducted in the Department of Hematology in collaboration with the Centre of Medical Genetics at the Sir Ganga Ram Hospital, New Delhi. It was a prospective observational study.

Study Population

25 cases with any of the myelodysplastic syndromes diagnosed as per the WHO classification, 2008 regardless of age were enrolled. During the study period, all the consecutively diagnosed patients in hematology formed the patient group.

Exclusion Criteria

Secondary causes of dysplasia including but not restricted to those detailed below were excluded as indicated.

i) Vit B_{12} and Folic acid deficiency.

ii) Infections like HIV, HBV, HCV, tuberculosis and Parvovirus B19.

iii) Significant history of intake of drugs associated with dysplasia or cytopenias (ATT, valproic acid, cotrimoxazole etc.).

iv) Chemotherapy, Radiotherapy or G-CSF therapy.

v) Paroxysmal nocturnal hemoglobinuria

vi) Heavy metal toxicity

vii) Congenital dyserythropoietic anaemia.

After obtaining informed consent, all patients underwent detailed history and physical examination.

The following investigations were carried out on the patients, as indicated:-

1. CBC, DLC, Peripheral Smear, reticulocyte count and ESR. Wright-Giemsa stained blood films were examined. ESR was measured by Westergren's technique
2. Renal Profile
3. Liver function tests
4. Chest X-ray
5. Iron Profile. Including serum iron, total iron binding capacity, transferrin saturation and ferritin levels
6. Vitamin B_{12} / Folic acid levels using Immulite competitive immunoassay
7. Viral serology: HIV, HbSAg, HCV, Parvo virus B19 serology.
8. Bone Marrow Aspiration and Biopsy: Bone Marrow aspiration slides were stained with Wright Geimsa stain and by other stains like cytochemical, immunochemical stains or iron stains wherever applicable. Bone marrow biopsy specimens were processed using 10% buffered formalin plus glacial acetic acid as fixative decalcifier solution and stained with Haematoxylin and Eosin as well as appropriate histochemical stains e.g, reticulin, as per requirement.
9. Cytogenetic study by conventional karyotyping /FISH: Bone marrow samples for cytogenetic studies were collected in freshly prepared Ham's F10 media supplemented with 20% FCS. The samples were processed by short term cultures for karyotypic chromosomal abnormalities. Fluorescence *in situ* hybridization (FISH) technique was used wherever feasible.

To assess the factors causing lag period in the diagnosis of MDS patients, a detailed, open-ended, informal interview was conducted covering onset of symptoms, reasons for seeking medical attention, the diagnostic work-up pursued and differential diagnoses generated and excluded. The reasons for non-performance of any diagnostic investigation were elicited and recorded. All patients' prior hospital records, whenever available were scrutinized and referral patterns analyzed.

Data Analysis

The data in each case was collected based on the proforma attached. Descriptive statistics was used for data analysis. Continuous variables are presented as mean ± SD or median (range). Categorical variables are expressed as frequencies and percentages. SPSS 17 for Windows statistics package (Microsoft Corp., Richmond, VA) was used for the analysis.

Results

The median age of the patients was 61 years, ranging from 6-77 years. The disease affected all the age groups with maximum number of patients in the age group of 61-80 years. Three patients (12%) were less than 20 years and formed the childhood MDS group. The males were 17(68%) and females 8(32%) with an M/F ratio of 2.1:1. The commonest presentation was anemia, seen in 24 patients (96%), followed by fever in 8 cases (32%) and bleeding in 6 patients (24%). Splenomegaly was seen in 2 patients (8%) and hepatomegaly in 1 patient (4%). No patient presented with lymphadenopathy. Blood products were required in 17 patients (68%). The median lag period to diagnosis was 6 months, ranging from 1-20 months. 10 patients (40%) had delayed diagnosis for more than 6 months.

The median hemoglobin was 7.7g/dl (range 5-12.2), median total leucocyte count 3.7×10^9/L (range 1.1-15.2), median absolute neutrophil count 1365/mm^3 (range 144-12616) and median platelet count 58×10^9/L (range3-406). The mean corpuscular volume was 95.5 fl (range 81-108); mean red cell distribution was 20.4% (range 13-35). Complete blood counts revealed that anemia was present in 22 patients (88%), neutropenia in 16 cases (64%) and thrombocytopenia in 16 patients (64%) as per WHO 2008 thresholds. Pancytopenia was common, seen in 11 patients (44%), followed by equal distribution of bicytopenia and unicytopenia in 7(28%) each. Peripheral Smear showed that anisocytosis was the commonest abnormality noted in 24 patients (96%), followed by macrocytosis in 17 patients (68%), pseudopelger Huet anomaly in 10 patients (40%). The circulating blasts were seen in 3 patients (12%).

The Bone Marrow was normocellular in 13 patients (52%) while it was hyper cellular in 7 patients (28%) and hypo cellular in 5 cases (20%). The erythroid maturation was normoblastic in 14 patients (56%) and megaloblastic in 11 patients (44%). Erythroid dysplasia [Figure 1] was seen in 19 patients (76%), myeloid dysplasia and megakaryocytic dysplasia [Figure 2] was observed in 20 patients each (80%) respectively. Megakaryocyte number was normal in 11 cases (44%), decreased in 11 patients (44%) and increased in 3 patients (12%). Bone marrow fibrosis was seen in one patient (4%) only. ALIPS (abnormal localization of immature precursors) were seen in 5(20%) patients with RAEB. Among the various WHO subclasses of MDS, refractory anemia with excess blasts (RAEB) was the commonest subtype. RAEB2 accounted for 40% of cases (n=10) with one patient showing associated fibrosis. RAEB1 was present in 8% of cases (n=2). RCMD and hypo plastic types of MDS accounted for 16% each (n=4). One case of childhood MDS was RCC (4%) that also had a hypo cellular marrow. Refractory anemia (RA), RARS, RT (RCUD), RCMD-RS were 4% (n=1) each [Figure 3].

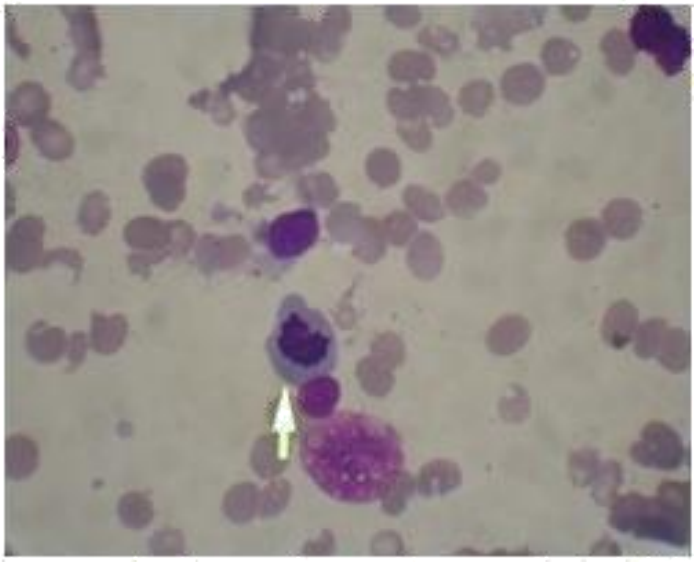

Figure 1: Bone marrow aspirate smears showing dyserythropoiesis (Geimsa, 100x).

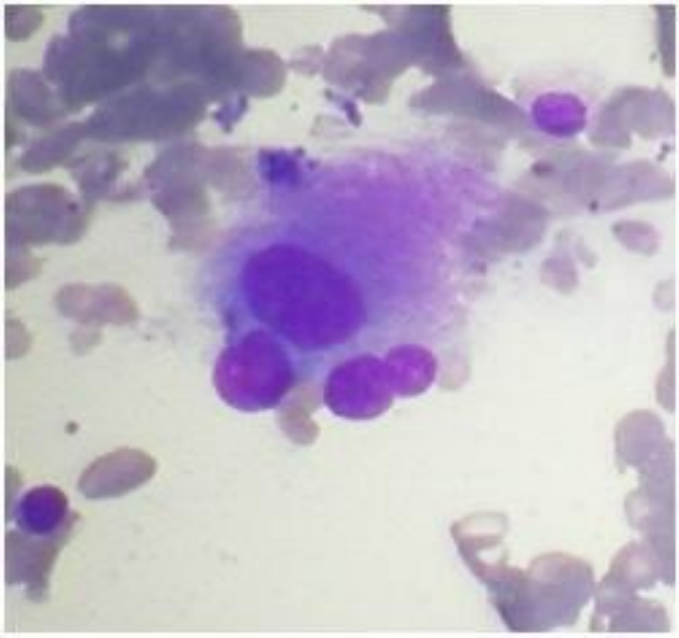

Figure 2: BM aspirate smears showing dysmegakaryopoiesis (Geimsa, 100x).

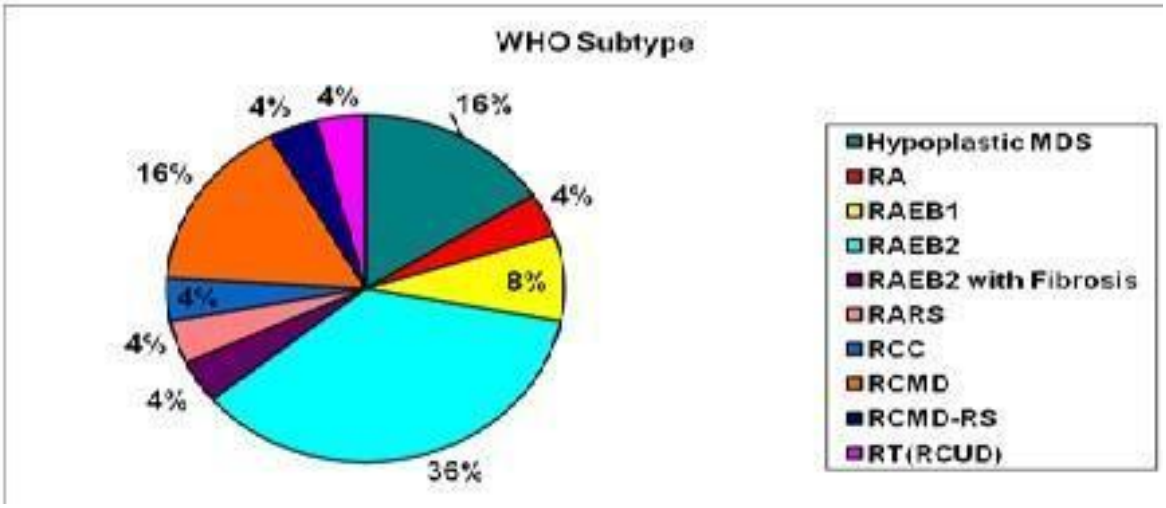

Figure 3: Pie Chart showing distribution of various WHO subtypes of MDS.

Bone marrow cytogenetics done by conventional karyotyping/FISH technique revealed that 9 patients (36%) had cytogenetic abnormality [Figure 4]. Complex cytogenetics was observed in 2 (8%) cases, del20q in 2 (8%) of patients, while as hyperploid, del5q, del12p; del5q, del1q; del9q, del5q and trisomy 10 with inversion 17 in 1 (4%) [Figure 5] each. Sixteen patients (64%) had a normal karyotype. Seven out of nine positive cytogenetics were found in RAEB. One each case of RCC and RT (RCUD) showed abnormal cytogenetics. Rest of the WHO subtypes did not reveal any cytogenetic abnormality. 15 (60%) cases had IPS of ≤1 (lower risk group), whereas 10 (40%) had score of >1 (higher risk group).

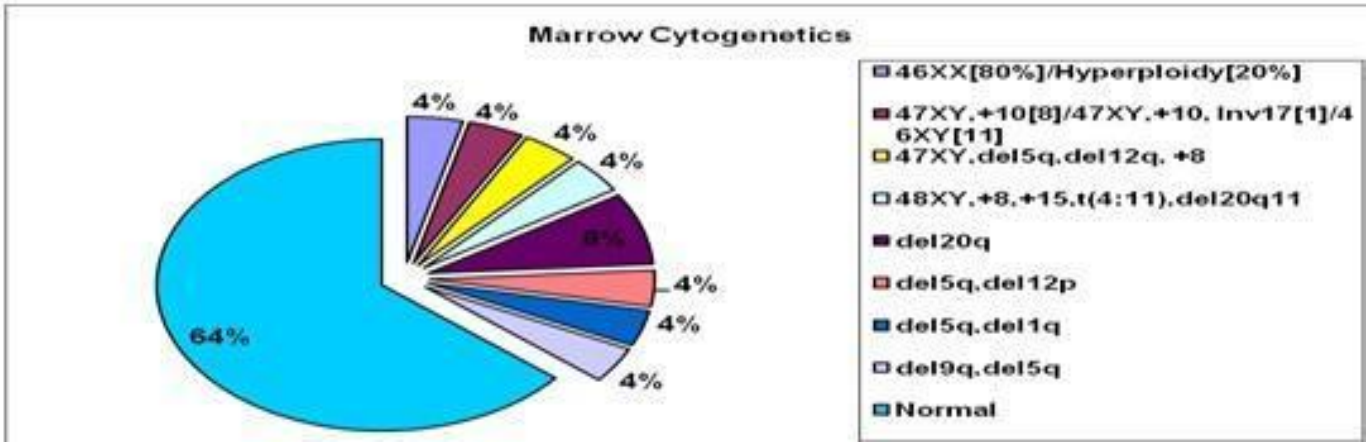

Figure 4: Pie Chart depicting distribution of marrow cytogenetics

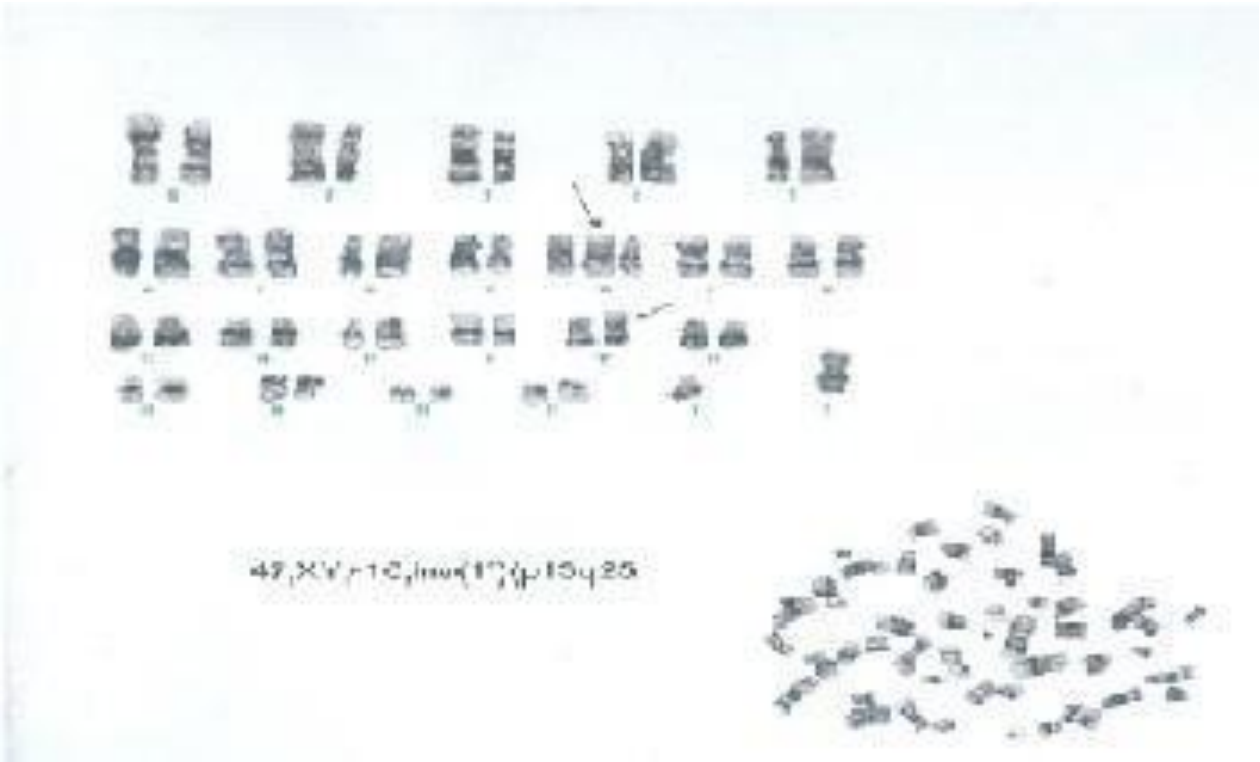

Figure 5: Cytogenetics done by metaphase karyotyping shows trisomy10 and inversion 17 (GTG Banding).

Out of total of 25 MDS patients, childhood cases were three in number with mean age of 11.6 years (range 6-16 years). Two were females and one male. All of them presented with anemia (100%). Fever and bleeding was seen in 2 cases each (66.7%). No patient had lymphadenopathy whereas hepatosplenomegaly was observed in one patient only. This case had RAEB2 WHO subtype. The mean Hb was 7.1 g/dl, median TLC 3.7×10^9/L, median ANC 1765/cu.mm, median platelet 19×10^9/L, mean MCV 89fl and mean RDW 17.3%. CBC revealed anemia and thrombocytopenia in all the 3 cases (100%) and neutropenia in 2 cases (66.7%) as per IPSS thresholds. Two patients presented with pancytopenia and one with bicytopenia. Peripheral smear showed anisocytosis in all three (100%) cases, macrocytosis in 1 patient (33%) and blast cells also in 1 case (33%) and no patient had psedopelger Huet anomaly. BM was hyper cellular in one, hypo cellular in other and normocellular in third. Erythroid maturation was normoblastic in 2 cases and megaloblastic in third one. Trilineage dysplasia was evident in all the three cases. Megakaryocyte number was decreased in two and normal in one. No patient had marrow fibrosis or ALIPS.

In the WHO subtype two patients had RAEB2 and one patient had RCC. Both the patients of RAEB2 had normal cytogenetics and one case of RCC had hyperploid. One child had an IPSS score of 1 (intermediate -1 risk group) and the other two had a score of 2 (Intermediate-2 risk group).

Discussion

The Myelodysplastic syndromes according to Western literature occurs over the age of 70 years. Our study revealed that the median age was 61 years, ranging from 6-77 years. This shows that MDS occurs almost a decade earlier than our Western counterparts and can affect any age group including children. The younger age corroborates with most of the Indian studies. Chatterjee et al. reported 45 years as the median age [5], Shah et al. documented 55 years as the mean age [6], while as Vundinti et al. showed the mean age as 44.3 years [7]. The reason for the younger age group in Indian population needs to be studied further. In our study males predominated over females with a male-female ratio 2.1:1. This predominance is almost consistent with Western literature and also with an Indian study by Chatterjee et al. [5], both of which showed an M/F ratio of 1.8:1.

Majority of our patients had anemia (96%) while as 32% had fever and 24% had bleeding. Organomegaly was rare (Splenomegaly 8% and hepatomegaly 4%). No patient presented with lymphadenopathy. Blood products in the form of packed red cells and platelet transfusions were required in 68% of the patients. These features are concordant to the Western literature [8]. Chatterjee et al. reported that pallor was the commonest complaint, followed by fever (52%) and bleeding (43%), however, hepatomegaly and splenomegaly was present in 49% and 28% respectively [5]. The higher incidence of hepatosplenomegaly in their study could in part be due to the fact that they included CMML as a type of MDS then.

The median duration of symptoms was 6 months, ranging from 1-20 months. 40% of the patients had a delay or lag of more than 6 months. The reasons for delay were multiple and included decreased awareness among the clinicians about this disease as most patients were treated elsewhere with either multivitamins or blood transfusion support for? Nutritional deficiency anemia or hypo plastic anemia. Other factors responsible were patient related e.g, poor economic status, and poor educational background, resorting to ayurvedic medications, refusing bone marrows and neglecting mild symptoms. Shah et al. [6] also reported the delay in the diagnosis (average of 358.8 days). This was attributed to the lack of diagnostic facility or lack of awareness among the clinicians [6].

Etiological factors of the MDS are largely unknown. However, possible agents include benzene exposure, cigarette smoking, agricultural chemicals or solvents and family history of hematopoietic neoplasms [9]. From India, Vundinti et al. reported higher frequency of MDS in patients exposed to pesticides [7]. In our study 4 out of 25 patients had history of cigarette smoking, but the cause and effect relationship could not be ascertained as our study was not a case control study. None had exposure to pesticides or chemicals or any family history of hematological malignancies.

Anemia of variable degree was present in majority of the patients with 88% having hemoglobin value of <10g/dl. The median hemoglobin was 7.7g/dl (range of 5-12.2g/dl), median total leucocyte count 3.7×10^9/L, median absolute neutrophil count 1365/mm^3 and median platelet count 58×10^9/L. Neutropenia (ANC<1.8×10^9/L) and thrombocytopenia (Plt<100×10^9/L) were observed in 64% of cases each. Pancytopenia was common (44%), followed by equal distribution of bicytopenia (28%) and unicytopenia (28%). The mean corpuscular volume was 95.5 fl, mean red cell distribution was 20.4% and mean reticulocyte count was 2.3%. On the other hand, Chatterjee et al. [5] reported mean Hb as 5.9g/dl, mean TLC as 7×10^9/L, mean ANC as 3500/mm^3, mean platelet count of 100×10^9/L [5]. Their commonest presentation was bicytopenia while as ours was pancytopenia. In Shah et al. [6] study pancytopenia was present in 37%, bicytopenia in 40.75%, anemia in 70%, leucopenia in 46.66% and thrombocytopenia in 53.33% of cases. In our study peripheral smear picked up anisocytosis as the commonest abnormality (96%), followed by macrocytosis in 68% of patients, pseudopelger Huet anomaly in 40% of patients and the blasts in 12% of patients. Chatterjee et al. [5] study revealed macrocytosis in 66.6% patients, pseudopelger Huet anomaly in 68.7% and circulating blasts in almost 20% cases.

Bone marrow aspirate/ biopsy are central to the diagnosis of MDS. The marrow cellularity is usually hyper cellular or normocellular, the cytopenias resulting from ineffective hematopoiesis. In our study, the bone marrow was normocellular in 52% of patients while it was hyper cellular in 28% patients and hypo cellular in 20% of patients. The figures are somewhat different from Shah et al. [6] study which showed hyper cellular marrow in 65.21%, normocellular in 8.66%, dry tap in 21.79% and hypo cellular in 4.34% of patients [6]. Chatterjee et al. [5] study revealed 22% normocellular marrow; ~ 40% hyper cellular marrow and 38% hypo cellular marrow.

Our study showed erythroid dysplasia in 76% of patients. Myeloid dysplasia and megakaryocytic dysplasia was observed in 80% of cases respectively. Erythroid dysplasia was present in the form of megaloblastic changes, karyorrhexis, multinuclearity and ring sideroblasts (2 cases). One patient with ring sideroblast had refractory anemia (RA) while as the other had RCMD. Myeloid dysplasia was present in the form of pseudo pelger Huet anomaly, decreased granularity, Auer rods and unusual size. Megakaryocytic dysplasia was evident in the form of multinucleation, micro megakaryocytes and nuclear hypolobation. Commenting on these features, Chatterjee et al. [5] reported dyserythropoiesis in 74% cases, dysmyelopoiesis in 69% cases and dysgranulopoiesis in 65% cases. Our study revealed that megakaryocyte number was normal in 44% cases, decreased in 44% and increased in 12% of patients whereas megakaryocytes were adequate in 34.78%, reduced in 30.43%, increased in 21.7% and absent in 13.03% in Shah et al study [6].

Significant degree of marrow fibrosis is seen in around 10% of MDS patients and this forms a distinct entity called MDS with fibrosis. Most of these cases have excess blasts and an aggressive clinical course [10]. Bone marrow fibrosis grade 2 was seen in one patient (4%) only in our study and it was associated with RAEB2. This is almost consistent with Chatterjee et al study which showed 3% bone marrow fibrosis of grade 2 in their patients [5]. ALIPS were seen in 20% cases and all in RAEB patients. This is consistent with Chatterjee et al study who demonstrated AL IPS in around 32% cases and all were RAEB cases [5].

The WHO 2008 classification of hematopoietic neoplasms subtypes MDS into various categories with RAEB the commonest category (40%), followed by RCMD (30%), RCUD (10-20%), RARS (3-11%). The other subtypes include isolated del5q and MDS unclassifiable. In accordance with WHO 2008 subtyping, we also found refractory anemia with excess blasts (RAEB) as the commonest subtype. RAEB2 accounted for 40% of cases and RAEB1 for 8% of cases. RCMD and hypoplastic types of MDS accounted for 16% each. One case of childhood MDS was RCC (4%). Refractory anemia (RA), RARS, RT (RCUD), and RCMD-RS were 4% each. In contrast to this, Chatterjee et al. [5] highlighted RA as the commonest subtype (63.54%) followed by RAEB (21.87%), RAEBT (5.2%), RARS (5.2%) and CMML (4.16%).

In our study, Bone marrow cytogenetics was done by either conventional karyotyping or FISH technique and it revealed that 36% had cytogenetic abnormality. This is slightly lower as compared to standard 50% positivity rate, although variable success rates have been reported across the globe. We found complex cytogenetics in 8% cases, del20q in 8% of patients, while as hyperploidy, del5q,del12p; del5q,del1q; del9q,del5q and trisomy 10 with inversion 17(rare cytogenetics in MDS) in 4% each. Del 5q was seen in four out of nine positive cases but not in isolation. Seven out of nine positive cytogenetics were found in RAEB. One each case of RCC and RCUD showed abnormal cytogenetics in the form of hyperploidy and del20q respectively. Our study emphasizes that cytogenetic abnormalities are more commonly seen in higher risk classes like RAEB and isolated single abnormalities are less frequent. This corroborates with Chinese study by Chen et al. [11] who analyzed 367 MDS patients cytogenetically and found the incidence of chromosomal abnormality increased with disease progression.

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