Original Article

A study of clinical, hematological and histomorphological profile of myelodysplastic syndromes

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Abstract

Background: Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by cytopenias, dysplasias, ineffective hematopoiesis and cytogenetic abnormalities with risk of transformation to acute myeloid leukemia. They have been classified into subtypes initially by the FAB scheme and later as per the WHO classification. **Objective:** To study the clinical, hematological and histomorphological features of patients diagnosed to have primary MDS. **Methods:** 30 adult cases of myelodysplastic syndrome were enrolled after excluding secondary causes of dysplasia, and their clinical, hematological and bone marrow morphology profiles were studied. They were classified into various subtypes according to the French-American-British (FAB) classification and the WHO 2008 classification. Cytogenetic profile could be done for 4 patients who were prognosticated according to IPSS scoring system. **Results:** The median age of MDS occurrence was 52 years. Male to female ratio of patients was 1.72:1. All patients had anemia. Leucopenia was seen in 12 cases (40%) and thrombocytopenia was seen in 16 (53.3%) patients. 10 patients had fever while 8 patients presented with bleeding symptoms. Refractory cytopenia with unilineage dysplasia (RCUD) was the commonest subtype (33.3%) of MDS followed by MDS-U as per WHO classification in our study, whereas as per FAB classification, Refractory Anemia (53.3%) was the commonest subtype. There were 5 cases of CMML. One patient had del (5q). There were no cases of RAEB-T. 96.6% patients had dyserythropoiesis, 46.6% had dysmyelopoiesis and 53.3% had dysmegakarypoiesis. Myelofibrosis was observed in 3 cases. **Conclusions:** MDS seems to occur earlier in Indian patients as seen in our study and in other Indian studies on MDS. The diagnosis of MDS remains a challenging one and so is the treatment. Cytogenetic analysis should be made more readily available and affordable to be able to prognosticate patients more accurately.

Keywords: Myelodysplastic Syndrome; Dysplasia; Cytopenias; Cytogenetics.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogenous group of stem cell disorders characterized by dysplasia, ineffective hematopoiesis, peripheral cytopenias and variable risk of transformation to secondary acute myeloid leukemia.[1] Incidence of MDS is around 4-5 per 1,00,000 yearly. It is one of the most common hematopoietic malignancies in people above 80 years of age.[2] MDS could be de novo (primary) MDS, secondary MDS or familial MDS. Exposure to cytotoxic drugs or therapeutic radiation is associated with increased risk of therapy-related MDS.[3] MDS is a clonal disorder of an early hematopoietic progenitor or stem cell. There is abnormality in maturation and differentiation of one or more hemopoietic cell lines i.e. erythrocytic, granulocytic or megakaryocytic. It evolves from an early phase of accelerated apoptosis resulting in ineffective hematopoeisis to a later phase of increasing proliferation with maturation arrest. This ineffective hematopoiesis accounts for the paradoxical coexistence of peripheral blood cytopenias despite a typically hypercellular bone marrow.[4] A minority of MDS patients have hypocellular

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bone marrow and they share an overlap of characteristics with aplastic anemia. These patients also have a better and durable response to immunosuppressive therapy.[5] Bone marrow cellularity in MDS ranges from ringed sideroblasts, megaloblastoid erythroblasts, myeloblasts, blasts in transition, pseudo Pelger-Huët abnormality of granulocytes, hypersegmented granulocytes, granulation abnormalities of granulocytes in the form of absent granules, Döhle bodies, abnormal localization of precursors (ALIP) and megakaryocyte abnormalities like hypogranulation or micromegakaryocytes. Chromosomal aberrations are present in half of all de novo MDS patients.[6] Cytogenetics in MDS range from normal karyotype to fusion oncogenes due to balanced translocations, unbalanced aberrations in chromosomes and complex karyotypes. Complex karyotype is defined in most studies as presence of minimum 3 independent chromosomal abnormalities in one cell clone.[7, 8] It is seen in around 15% of MDS patients and is regarded to have a worse prognosis. Clinical features of MDS are due to cytopenias. Patients may present with fatigue, breathlessness, and palpitations due to anemia. Petechiae, ecchymoses, gum bleeding, epistaxis can occur due to thrombocytopenia while fever, infection may occur due to leucopenia. However, at least half of the patients may be asymptomatic, and their MDS is discovered incidentally on routine blood counts. Risk factors for MDS are radiation exposure, genotoxic industrial chemicals, heavy metals, genetic disorders like Down's syndrome, congenital disorders like Neurofibromatosis-1, Shwachman –Diamond syndrome, DNA repair deficiency like Fanconi anemia.

Classification of MDS

MDS was classified in 1982 as per French- American - British (FAB) cooperative group scheme.[9] In 2001, the FAB guidelines were revised and updated in the World Health Organization (WHO) Classification of MDS.[10]

Table 1: French – American – British Classification Criteria

Subtype	Peripheral Blood	Bone Marrow
Refractory anemia (RA)	Blasts <1%	Blasts <5%
Refractory anemia with ringed sideroblasts (RARS)	Blasts <1%	Blasts <5%, and >15% ringed sideroblasts
Refractory anemia with excess blasts (RAEB)	Blasts <5%	Blasts 5%–20%
Refractory anemia with excess blasts in transformation (RAEB-T)	Blasts >5%	Blasts 20%–30% or Auer rods
Chronic myelomonocytic leukemia (CMML)	Monocytes >1 × 10^9/L	Any of the above
Acute myelogenous leukemia (AML)		Blasts >30%

Source: Bennett *et al* [9]

In 2008, WHO revised its classification to include cases of MDS who could not be subclassified according to its earlier scheme and to allow for more clinically relevant classification of patients who were falling in the 'MDS – unclassifiable' category. It incorporates clinical features, peripheral blood and bone marrow findings, and cytogenetic analysis.[10] It also includes a collection of neoplasms that share features of MDS and myeloproliferative neoplasms (MDS/ MPN). These include CMML, Atypical CML, Juvenile myelomonocytic leukemia and MDS/ MPN-unclassifiable.

Table 2: WHO 2008 Classification of MDS [10]

Sr. No.	Disease	Blood Findings	Bone Marrow Findings
1	Refractory cytopenias with Unilineage dysplasia (RCUD)	Unicytopenia	Unilineage dysplasia in ≥ 10% of the cells <5% blasts
2	Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only <5% blasts ≥ 15% ringed sideroblasts
3	Refractory cytopenias with multilineage dysplasia (RCMD)	Cytopenias No blasts (<1%)	Dysplasia in ≥10% of cells in two or more myeloid lineages <5% blasts
4	Refractory anemia with excess blasts-1 (RAEB -1)	Cytopenias <5% blasts	5-9% blasts
5	Refractory anemia with excess blasts -2 (RAEB-2)	Cytopenias 5 – 19 % blasts	Unilineage or multilineage dysplasia 10 –19 % blasts
6	Myelodysplastic syndrome – Unclassified (MDS – U)	Cytopenias No or rare blasts	Unequivocal dysplasia in ≤ 10%
7	MDS associated with isolated Del (5q)	Anemia No or rare blasts (<1%) Platelet count Usually normal or increased	5q31 deletion Anemia, hypolobulated megakaryocytes, <5 % blasts

In the present study, we assessed the clinical, hematological and histomorphological features in 30 patients of primary MDS and subtyped patients according to FAB and WHO 2008 classifications.

MATERIALS AND METHODS

This study was carried out in a tertiary care centre. 30 adult patients who were diagnosed as primary MDS during their course of workup for refractory cytopenias were included in this cross-sectional study. Their demographic details were recorded. They were evaluated by clinical history, family history and physical examination.

Exclusion Criteria

Other causes of cytopenias and dysplasia were ruled out wherever indicated as below:

- Vitamin B12 and Folic acid deficiency,
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Chemotherapy
- Infective causes like tuberculosis and anti-tuberculous therapy
- Congenital dyserythropoietic anaemia

Routine blood investigations like CBC, peripheral blood smear examination, liver and renal function tests, blood sugars, chest X rays, ECG were done in the enrolled patients. Peripheral smears were stained by Giemsa stain. All patients underwent bone marrow aspiration and biopsy which were stained by hematoxylin and eosin. Special stains were used to demonstrate ringed sideroblasts and reticulin fibres. Bone marrow was assessed for cellularity, dysplasia, fibrosis, ALIP (Abnormal localization of immature precursors). Cytogenetic studies could be performed in only 4 patients due to financial constraints. MDS was defined as refractory cytopenias/s plus dysplasia in one of the hemopoietic cell lineages. Other causes of cytopenias were ruled out. Anemia was defined as Hb less than 13 g% in men and less than 12 g% in women. Patients were classified as mild anemia (Hb- 10 -12 g %), moderate anemia (Hb- 8-10 g %) and severe anemia (Hb < 8g %). Leucopenia was defined as WBC count < 4000/cmm. Leucocytosis was defined as WBC count >11,000/cmm. Thrombocytopenia was defined as platelet count < 1.5 lakhs/cmm. CMML was defined as peripheral blood monocytosis > 1000 monocytes/μL. Bone marrow dysplasia was defined as >10% of precursors of myeloid lineage showing dysplastic features. Dysplasia was defined as abnormal shape, appearance and morphology of cell. Ring sideroblasts were defined as erythroblasts with iron-loaded mitochondria visualized by Prussian blue staining (Perls reaction) as a perinuclear ring of blue granules. Patients were classified into different groups based on FAB classification as well as the WHO 2008 classification. IPSS (International Prognostic Scoring System) was used to stratify the MDS patients into 4 risk groups (Low, Intermediate -1, Intermediate -2 and High risk). IPSS prognostic scoring was applied to the 4 patients in whom cytogenetic studies could be done. Treatment was initiated as per NCCN guidelines. Patients were given supportive treatment in the form of blood products, iron chelation, EPO, G-CSF, antibiotics. Immunosuppressive therapy included Danazol, ATG, cyclosporine, hydroxyurea, steroids. Monosomy 7 patients received chemotherapy (Cytarabine). Patients with del5q received lenalidomide which is an immunomodulator and antiangiogenic agent. All patients received supportive therapy with red blood cell transfusions, folic acid and Vit. B12 supplements.

RESULTS

30 patients of primary MDS were enrolled in the study. The age range was from 22 years to 83 years. Median age was 52 years. 19 patients (63.3%) were in age group of less than 60 years, while 11 patients (36.6%) were in age group more than 60 years. 8 patients were below age of 40 years. Commonest age of presentation was 40-60 years (36.6%). Out of the 30 patients, there were 19 males (63.3%) and 11 females (36.6%). Male to female ratio was 1.72:1. All 30 patients presented with symptoms of anemia and had pallor, followed by fever in 10 (33%) cases and bleeding in 8(26%) cases. Combined clinical features of anemia and fever were found in 33.3% patients. Anemia associated with fever and bleeding was seen in 3 cases (10%). Hemoglobin ranged from 3.1 to 10.4 gm%. WBC ranged from 1.7 – 125.5 x 10^9/L. Leucopenia was seen in 12 cases (40%). Platelet count ranged from 0.11 – 142.8 x 10^9/L. Thrombocytopenia was seen in 16 (53.3%) patients. 73.3% patients had severe anemia while (26.6%) had moderate anemia. 40% of patients had leucopenia. All 5 CMML patients (16.6%) had WBC count of more than 11000 cells/cmm with monocytosis ranging from 13.38-48.96×10^9/L. 53% patients had thrombocytopenia, out of which 8 patients presented with bleeding. One patient with del (5q) had platelet count of 14,90,000 cells/cmm.

Table 3: Characteristics of MDS patients

Age in years	Number of patients	Percentage %
20-40	8	26.6%
40-60	11	36.6%
60-80	10	33.3%
More than 80	1	3.33%
Sex		
Male	19	63.3%
Female	11	36.6%
Clinical features		
Anemia	30	100%
Fever	10	33.3%
Bleeding	8	26.6%
Anemia + fever	10	33.3%
Anemia + bleeding	8	26.6%
Anemia + fever + bleeding	3	10%
Anemia		
Mild	0	0%
Moderate	8	26.6%
Severe	22	73.3%
WBC count/cmm		
Less than 4000	12	40%
4000-11000	13	43.3%
More than 11000	5	16.6%
Platelet count/cmm		
Less than 1.5 lakhs	16	53.3%
More than 1.5 lakhs	14	46.6%

According to FAB classification of the subjects, 16 patients (53.3%) had refractory anemia which was the commonest subtype followed by CMML in 5 patients (16.6%). 6.66% patients had RAEB. None of the patients were in RARS, RAEB-T subgroup. There were 3 cases (10%) of myelofibrotic MDS, 4 cases (13.33%) of hypoplastic MDS. These could not be classified according to FAB classification.

Table 4: Classification of MDS patients as per FAB scheme

Subtype	Number of patients	Percentage %
RA	16	53.3%
RARS	0	0%
RAEB	2	6.66%
RAEB-T	0	0%
CMML	5	16.66%

According to WHO classification of patients, Refractory Cytopenia with Unilineage dysplasia (RCUD) was the commonest subgroup (33.3%) followed by MDS-U (23.3%). Out of 7 patients in MDS-U subgroup, 3 had myelofibrotic MDS and 4 had hypoplastic MDS. 5 patients (16.6%) of CMML were in MDS/MPN subgroup. One patient had del (5q).

Table 5: Classification of MDS patients as per WHO 2008 scheme

Disease	Number of patients	Percentage %
RCUD (RA,RN,RT)	10	33.3%
RARS	0	0%
RCMD	4	13.3%
RAEB-1	2	6.67%
RAEB-2	1	3.33%
MDS-U	7	23.3%
Del (5q)	1	3.33%
MDS/MPN	5	16.66%

Table 6: Hepatomegaly and/or splenomegaly

Subtype	Number of patients	Percentage %
RA	2	6.66%
RCMD	1	3.33%
Myelofibrotic MDS	1	3.33%
CMML	4	13.3%

Hepatomegaly and/or splenomegaly were seen in 8 (26.6%) cases out of 30, but they were commonly found in CMML patients (13.3%).

Table 7: Bone marrow histomorphology

Bone marrow features	Number of patients	Percentage %
Cellularity		
Normocellular	12	40%
Hypercellular	11	36.6%
Hypocellular	7	23.3%
Dyspoiesis		
Dyserythropoiesis	29	96.6%
Dysmyelopoiesis	14	46.6%
Dysmegakaryopoiesis	16	53.3%

12 patients (40%) had normocellular marrow. 11 patients (36.6%) had hypercellular marrow. 7 patients (23.3%) had hypocellular marrow; they were distinguished from aplastic marrow by the presence of dysplasia. Dyserythropoiesis was seen in all cases except in one case of del (5q). Abnormal location of immature precursor (ALIP) was present in one patient.

Table 9: Cytogenetics of 4 patients

Patient No.	MDS subtype	Karyotype	Prognostic subgroup
1	RA	46XY,invY 43XY-7,-14,-15 47XY-16 47XY del4q21	Poor
2	Hypoplastic MDS	45XY, t(2:18) Del3q21 -17	Intermediate
3	Hypoplastic MDS	Monosomy 7	Poor
4	RA	Del5q	Good

Cytogenetic studies were done in 4 patients. Karyotype of patient with del (5q) was classified as good, while monosomy 7 and complex karyotype (3 or more cytogenetic abnormalities) were classified as poor prognostic subgroups. Philadelphia chromosome was absent in all 5 cases of CMML.

Table 10: IPSS score and risk groups

Sr. No.	BM blast %	Blood cytopenias	Karyotype	IPSS score	Risk group
1	0	2	Poor	1	Intermediate-1
2	0	3	Intermediate	1	Intermediate-1
3	3	3	Poor	1.5	Intermediate-2
4	0	1	Good	0	Low

IPSS score done in all 4 patients wherein cytogenetic studies were done. Patient having del (5q) was in low risk group denoting good prognosis, median survival of 5.7 years and median time to 25% AML evolution of 9.4 years. Patient with monosomy 7 was in Intermediate-2 risk group denoting poor prognosis, median survival of 1.2 years and median time to 25% AML evolution 1.1 year.

Table 11: IPSS: Survival and AML evolution [19]

IPSS score	Risk group	Median survival (years)	Median time to 25% AML evolution (years)
1	Intermediate-1	3.5	3.3
1	Intermediate-1	3.5	3.3
1.5	Intermediate-2	1.2	1.1
0	Low	5.7	9.4

DISCUSSION

Traditionally, MDS is thought to be a disease of the elderly. Most of the data on MDS comes from the western literature. Study by Aul C. *et al* indicates that as the age increases the incidence of MDS increases.[3] In a study from India by Chatterjee *et al*, the median age of MDS patients was reported as 45 years.[12] In the study by S. Nigam *et al*, there were 75.7% patients less than 60 years of age.[13] In our study the median age of MDS patients was 52 years which is consistent with the findings of a relatively younger age of occurrence of MDS in most of the Indian studies.[12, 13] There were 19 males and 11 females in our study with a male to female ratio of 1.72:1 indicating male predominance of the disease and is comparable to male predominance ratios of 1.8:1 observed in studies by Chatterjee *et al* [12] and 1.7:1 by Dakshinamurthy *et al* [15]. Similar male predominance was also reported by Van Der Weide *et al*.[14] Anemia was present in all the patients. Leucopenia was seen in 12 patients (40%). Thrombocytopenia was seen in 16 patients (53.33%). Hepatomegaly and splenomegaly were present in CMML, RA, RCMD and myelofibrotic MDS but observed more commonly in CMML patients (13.33%). CMML is known to cause infiltration of skin, liver, spleen and gingiva.[16] This could be the reason for presence of hepatomegaly and splenomegaly in the CMML group of patients in our study. In our study, 16 cases (53.33%) belonged to Refractory Anemia (RA) group according to FAB classification. Similarly, RA was the commonest type of MDS (32 out of 101 cases) in a study by T. Vallespi *et al*.[17] No case of RARS was found similar to the study by S. Nigam *et al*.[13] Nair *et al* had reported RAEB-T as the commonest type of MDS in their study (32 out of 88 cases). However, no cases of RAEB–T were found in our study. It may signify early presentation, early diagnosis or may be due to small number of patients in our study. As per the WHO 2008 classification of hematopoietic neoplasms[10], in MDS, RAEB is the commonest category (40% followed by RCMD (30%), RCUD (10-20%), RARS (3-11%). However, in our study, according to the WHO 2008 classification, we found that RCUD was the commonest subtype (33.3%). Bone marrow was normocellular in 14 cases (46.67%), hypercellular in 11 (36.67%) and hypocellular in 5 cases (16.66%). Chatterjee *et al*[12] in their study found 22% normocellular marrow; 40% hypercellular marrow and 38% hypocellular marrow. ALIP which is diagnostic but not specific feature of MDS was found in only one patient. Presence of ALIP predisposes patient to development of acute myeloid leukemia and is considered to carry a worse prognosis.[18] Myelofibrosis was observed in 3 cases (10%) demonstrated by silver stains. In our study there was erythroid dysplasia in 96.6% cases. It was in the form of megaloblastoid changes and karyorrhexis. Karyotyping done in 4 cases helped to detect 5q- syndrome in one patient. It also helped to calculate the IPSS score in these patients and identify the risk group which guides the treatment. Cytogenetic studies could not be done in all the patients which is a limitation of this study.

CONCLUSIONS

Myelodysplastic syndromes are among the most challenging myeloid neoplasms to diagnose and classify. Incidence of MDS is increasing due to increase in elderly population and improved recognition. Our study showed early onset of MDS by 6th decade in Indian patients as compared to Western patients with MDS. There was male preponderance, and anemia dominated the clinical features. We classified patients according to the FAB classification as well as the WHO 2008 classification and accordingly, RA and RCUD were respectively the commonest subgroups in MDS patients. The role of FAB/WHO staging and IPSS scoring to stratify patients into risk groups for estimating median survival is important. Cytogenetic studies should be made more readily available and affordable to be able to accurately prognosticate patients as per the IPSS system. Molecular research and development of new drugs will contribute to improved survival and better quality of life in MDS patients.

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