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Original Article

Clinicopathological profile of myelodysplastic syndrome (MDS) with monosomy 7 and deletion 7q: An institute experience

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ABSTRACT

Objective: Assessment of clinicopathological and bone marrow parameters in Myelodysplastic Syndrome (MDS) with monosomy 7 and deletion (del) 7q and their prognostic stratification.

Material and Methods: Retrospective observational study of MDS patients with monosomy 7 and deletion (del) 7q was conducted from January 2013 to August 2021. Demographic, clinical, and hematological variables were acquired apart from cytogenetic analysis and karyotyping. Prognostic International Prostate Symptom Score (IPSS) risk stratification was performed.

Results: 110 patients of MDS underwent cytogenetics study, 8 patients had monosomy 7, and 17 patients had del 7q. The median age group for both subsets was 51–54 years. Both groups showed male predominance. In monosomy 7 MDS, severe anemia was more profound (87%) in comparison to del 7q (53%). Absolute neutrophil count (ANC) of <800/cubic mm was found equally in both groups. 88% of both the subsets had platelet count <50 thousand/liter with higher Lactate Dehydrogenase (LDH) in the del 7q group (81.25%). About 50% of MDS cases with monosomy 7 and 37.5% of del 7q cases had excess blasts of > 5%. Based on the Revised International Prognostic Scoring System (IPSS-R), 75% of patients in both subsets had a high and very high-risk category. Progression to Acute myeloid leukemia (AML) was more common in monosomy 7 than in del 7q (23% vs 24 %).

Conclusion: Early age of presentation with predominance in men was noted in both the groups. The IPSS-R score was more valid in determining the risk category for predicting the course of these patients rather than considering cytogenetic type alone. However, more cases need to be analyzed to validate our findings.

Keywords: Monosomy 7, Myelodysplastic Syndrome, Deletion 7q

INTRODUCTION

The Myelodysplastic Syndrome (MDS) is a group of clonal hematopoietic stem cell diseases characterized by cytopenia, dysplasia in one or more of the major myeloid lineages, ineffective hematopoiesis, recurrent genetic abnormalities, and an increased risk of developing acute myeloid leukemia (AML).[1-3] The classification of MDS is continuously evolving, and the prognosis is largely dependent on the presence of chromosomal abnormalities.[4] The revised 2016 WHO diagnostic criteria are used for the classification of MDS and include MDS with single lineage dysplasia (MDS-SLD), MDS with multilineage dysplasia (MDS-MLD), MDS with ring sideroblasts (MDS-RS), MDS with excess blasts (MDS-EB1 and 2), MDS with isolated del(5q), and MDS unclassifiable (MDS-U). Refractory cytopenia of childhood (RCC) is considered a provisional entity. The Revised International Prognostic Scoring System (IPSS-R) takes into account karyotype, bone marrow blast percentage, hemoglobin concentration, platelets, and absolute neutrophil count.

Chromosomal abnormalities are detected in approximately 50% of patients with de novo MDS and up to 80% of patients with MDS secondary to chemotherapy or other toxic agents.[5] Abnormalities involving chromosome 7 occur in approximately 20% of patients with MDS and clonal cytogenetic abnormalities and usually include deletion (del) of part of the long arm of chromosome 7 (7q), total loss of chromosome 7 (monosomy 7), or translocations involving chromosome 7.[6] IPSS-R considers del7q patients as having intermediate-risk cytogenetics (score 2), and monosomy 7 patients as having poor-risk cytogenetics (score 3).[7] The present study aims to assess the clinical features, hematological

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parameters, and bone marrow morphology in patients with del 7q and monosomy 7 and also to categorize them into prognostic groups.

MATERIAL AND METHODS

This retrospective observational study was conducted on patients with de novo or previously diagnosed MDS who presented in the Hematology Division of the Oncopathology Department, Gujarat Cancer Research Institute, from January 2013 to August 2021. The cases without cytogenetic studies were excluded from the study. The patient details were obtained from the electronic medical records as well as from case files. Approval from the Institutional Ethical Committee was obtained.

The diagnosis was made based on the blood parameters, clinical characteristics, and bone marrow findings. Cytogenetic analysis and karyotyping were also performed. Prognostic risk stratification was done according to revised IPSS criteria.

The May Grunwald Giemsa (MGG) stained bone marrow aspirates and Hematoxylin and Eosin (H&E) stained bone marrow sections were reviewed, and the morphological details were recorded.

Fluorescence in situ hybridization (FISH) was performed on heparinized bone marrow aspirate on the first tap. Colcemid, followed by a hypotonic solution, was added to the samples. Slides were prepared from the harvest by the air-dry method and processed for FISH. Using a phase-contrast microscope, the area of interest was determined, followed by denaturation and hybridization, and finally scanned under a fluorescent microscope using suitable filters for DAPI(4′,6-diamidino-2-phenylindole), spectrum orange, and spectrum green signals. The raw images were saved in a software-specific file format, and the final image analysis and interpretations were made.

Karyotyping was performed on heparinized bone marrow aspirate from the first tap using the Giemsa banding (GTB-banding) technique. Karyotypes were described with reference to the International System of Human Cytogenetic Nomenclature (ISCN) 2016. Statistical analysis was performed on the collected data using standard statistical software.

RESULTS

A total of 180 MDS patients were included in our study. The cytogenetic study was available for 110 (61%) patients. Twenty five patients (approximately 23%) had chromosome 7 abnormalities, with monosomy 7 in 8 patients and del 7q in 17 patients. Two patients from either of the categories had additional chromosomal abnormalities.

Our study showed MDS with monosomy 7 and del 7q abnormalities was more common in the age group of 50–54 years and men (5/8 and 13/17 cases, respectively).

In MDS with monosomy 7, severe anemia of <8 g/dL was found to be more frequent (87%) in contrast to del 7q (53%). Nearly 40% of both groups had an absolute neutrophil count (ANC) of $<0.8 \times 10^3$/cumm. Thrombocytopenia with a platelet count less than 50×10^9/liter was a common finding, accounting for nearly 88% of either subset. Serum Lactate Dehydrogenase (LDH) was raised (>280 U/L) more in del 7q cases (13/16, 81.25%) in comparison to monosomy 7 cases (3/8, 37.5%). No statistically significant difference was found between the two groups. The patient's clinicopathological characteristics are shown in Table 1.

Bone marrow hypercellularity was more common in the monosomy 7 subsets (4/8 cases, 50%) as compared to the del7q subset (6/17 cases, 35%). Eosinophilia was observed in 3 cases (37.5%) of the monosomy 7 group and 5 cases (29%)

Table 1: Clinicopathological features of the two groups of MDS.

Patient characteristics	Monosomy7	Del 7q
	No of cases (%)	No. of cases (%)
Median age (in years)	51	54
Gender		
Men	5(62.5)	13(76.4)
Women	3(37.5)	4(23.5)
MDS subtype		
MDS-SLD	3(37.5)	2(11.7)
MDS-MLD	1(12.5)	6(35.3)
MDS-EB		
MDS-EB1	1(12.5)	1(5.8)
MDS-EB2	2(25)	7(41.2)
MDS-U	1(12.5)	NIL
RCC	NIL	1(5.8)
HB (g/dL)		
<8	7(87.5)	10(58.8)
8–10	1(12.5)	7(41.2)
>10	0	0
ANC ($\times 10^9$/L)		
<0.8	3(37.5)	7(41.2)
>0.8	5(62.5)	10(58.8)
Platelet ($\times 10^9$/L)		
<50	7(87.5)	15(88.2)
50–100	0(0)	2(11.7)
>100	1(12.5)	0(0)
Raised LDH	3(37.5)	13/16(81.25)

MDS: Myelodysplastic syndrome, MDS-SLD: Myelodysplastic syndrome-single lineage dysplasia, MDS-MLD: Myelodysplastic syndrome-multilineage dysplasia, MDS-EB: Myelodysplastic syndrome-excess blast, MDS-EB 1: Myelodysplastic syndrome-excess blast 1, MDS-EB 2: Myelodysplastic syndrome-excess blast 2, MDS-U: Myelodysplastic syndrome-unclassifiable, RCC: Refractory cytopenia of childhood, HB: Hemoglobin, ANC: Absolute neutrophil count, LDH: Lactate dehydrogenase

of the del7q group. Dysplasia involving single or multiple lineages was observed as shown in Table 2. Fifty percent of the cases with MDS with monosomy 7 showed a higher number of blasts (>5%) than the del 7q cases (37.5%). Marrow fibrosis was equally observed in both categories. The bone marrow findings are shown in Table 2 and Figures 1a–d.

Two cases of monosomy 7 MDS had additional aberrations, namely trisomy 1q and deletion of the long arm of chromosome 6 along with an unbalanced translocation between 13 and 21. Similarly, two cases of del7q had additional aberrations, namely, isochromosome 7 and complex chromosomal abnormalities. The latter case of del7q also had a history of colon carcinoma four years back for which she had chemotherapy and lower anterior resection. Based on the IPSS-R, 75% of the patients in both subsets were in high- and very high-risk categories. Individual cases of both groups were further categorized into WHO subgroups [Table 1] and risk groups based on the IPSS-R stratification [Table 3].

Table 2: Bone marrow findings in the two groups of MDS.

Cellularity		
Normocellular	1(12.5)	7(41.1)
Hypocellular	3(37.5)	4(23.5)
Hypercellular	4(50)	6(35.3)
Eosinophilia	3(37.5)	5(29.4)
Basophilia	1(12.5)	1(5.8)
Dyserythropoiesis	1(12.5)	1(5.8)
Dysgranulopoiesis	2(25)	0(0)
Dysmegakaryopoiesis	2(25)	4(23.5)
Dyserythropoiesis + Dysgranulopoiesis	1(12.5)	3(17.6)
Dysgranulopoiesis + Dysmegakaryopoiesis	0(0)	1(5.8)
Dyserythropoiesis + Dysmegakaryopoiesis	0(0)	2(11.7)
Trilineage Dysplasia	2(25)	6(35.3)
Blasts in Bone Marrow		
<2%	3(37.5)	3(17.6)
>=2 to <5%	2(25)	5(29.4)
5-10%	1(12.5)	4(23.5)
>10%	2(25)	5(29.4)
Marrow Fibrosis	2(25)	4(23.5)

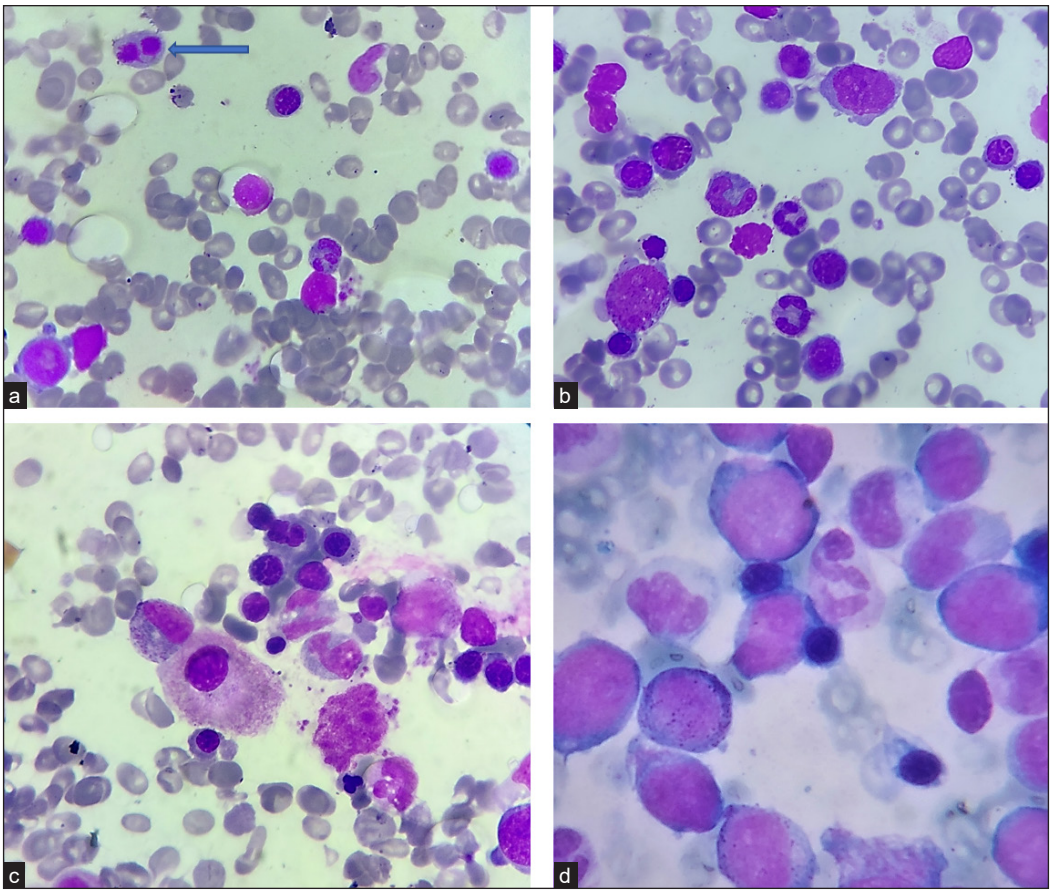

Figure 1: Photomicrograph demonstrating (a) nuclear bridging in a dyserythropoietic cell shown by an arrow May-Grunwald-Giemsa (MGG, X-400), (b) dysgranulopoietic cell showing giant and hypogranulated granulocytes. (MGG, X400), (c) dysmegakaryocytic cell with hypogranulation and hypolobation shown by an arrow (MGG, X400), and (d) increased number of blasts (MGG, X1000).

Table 3: Distribution of cases into the IPSS-R risk group.

	Very low	Low	Inter-mediate	High	Very high
MDS with isolated monosomy 7	N/A	N/A	2	3	1
MDS with monosomy 7 and additional aberration	N/A	N/A	0	0	2
MDS with isolated del 7q	N/A	N/A	4	4	7
MDS with del 7q and additional aberration	N/A	N/A	0	0	2

IPSS-R: Revised International Prognostic Scoring System, MDS: Myelodysplastic syndrome

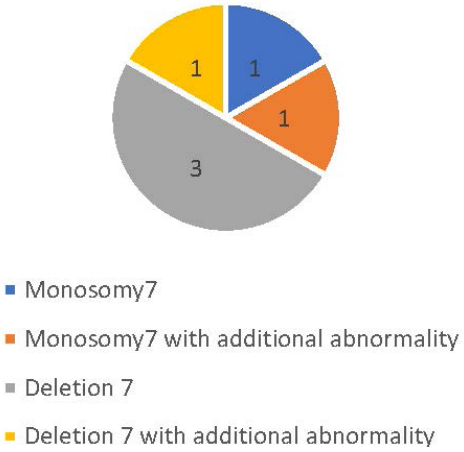

Figure 2: Pie diagram showing the number of cases that transformed to Acute myeloid leukemia.

AML transformation was noted in six cases, as depicted in Figure 2. In the MDS monosomy 7 group, two out of eight patients (23%) and in the MDS deletion 7q, four out of 17 patients (approximately 24%) developed AML with a median time of progression of 3.5 and 4.5 months, respectively. Among the cases converting to AML, one of the monosomy 7 cases had trisomy 1q, and one of the del 7q cases had isochromosome 17. Decitabine /Cytarabine and lenalidomide remained the mainstays of treatment for both groups. Erythropoietin and blood transfusions were also given in most of the cases. In the AML transformed cases, a 7+3 chemotherapy regimen was given. Stem cell transplantation was done only in one of the monosomy 7 cases, but she died of a lung infection 4 days after transplantation. Four (2 cases from each group) out of the total of six AML transformed patients succumbed to death. Follow-up data were available for 21/25 patients with 4 patients lost to follow-up.

DISCUSSION

In our study, chromosome 7 abnormalities (monosomy 7/del7q) were present in about 23% of the MDS patients, which was slightly higher than the frequency of 11.7–14.2% in two large Indian studies.[8,9] We found that the median age of presentation for patients with MDS with monosomy 7 and del 7q was 51 and 54 years, respectively. These results were in contrast with some other studies, where the median age of presentation was about 65 years.[10,11] Male predominance was noted in both groups as in most of the studies.[12] Crisa *et al.* found a lower platelet count in the monosomy 7 group than in the del 7 groups, however, Hb and ANC were found to be similar in both groups.[11] In contrast, our study found severe anemia to be more frequent in the MDS-monosomy 7 subset and a similar occurrence of thrombocytopenia and neutropenia in either of the groups. Cordoba *et al.* found that low hemoglobin, platelet count, and ANC were more common in the isolated monosomy 7 group, and additional chromosomal abnormalities worsened the prognostic consequences.[10] Bone marrow eosinophilia/basophilia has been significantly associated with chromosomal 7 abnormalities in some earlier studies.[13] No such findings were noted in our study. Dysplasia involving erythroid, myeloid, and or megakaryocytic lineages was found in both groups. Honda *et al.* demonstrated in mice, that the homozygous and heterozygous loss of the sterile motif (SAM) domain-9 (Samd9L) gene on chromosome 7, resulted in peripheral blood cytopenias and marked dysplasia and further elucidated the direct impact of various genes on chromosome 7 and the morphological spectrum of MDS/AML.[14] In the present study, blasts >5% were identified in 3 cases (37.5%) and 9 cases (52%) of MDS monosomy 7 and del 7q, respectively with approximately similar risk of transformation to AML. Patients with blast >5% at presentation had a significantly higher risk of transformation to AML than those with blast <5%. The percentage conversion of cases to AML in either of the subsets was the same (nearly 24%) in the present study. According to most of the studies, del 7q and monosomy 7 are considered to be of intermediate and poor-risk categories, with a better prognosis for the patients with the former cytogenetic abnormality than the latter.[7,10] However, the presence of additional cytogenetic aberrations also affects the outcome. One of our del 7q cases, which showed leukemic transformation also had isochromosome 17, which is classified as an intermediate cytogenetic subgroup as per the IPSS-R and as an adverse cytogenetic subgroup as per the revised Medical Research Council classification for AML. Complex chromosomal rearrangement and trisomy 1q were among the additional abnormalities found in MDS patients with del7q and monosomy 7, respectively, which are again associated with

aggressive clinicopathological features. Crissa E *et al*. found blast count, TP53 mutations, and several other mutations to be independent predictors of overall survival and that the cytogenetic subgroups did not retain prognostic relevance.[11] Some studies stated that, independent of established risk factors, somatic mutations involving Tumor protein 53 (TP53), Enhancer of zeste homolog 2 (EZH2), ETS variant transcription factor 6 (ETV6), Runt-related transcription factor 1 (RUNX1), Additional sex combs like 1 (ASXL1) are predictors of poor overall survival in MDS patients.[15,16] Our study included patients in intermediate, high, and very high-risk groups with treatment in the form of hypomethylating agents, lenalidomide, and supportive care. Though stem cell transplantation is considered the preferred treatment in high-risk MDS, because of the poor socio-economic status of the patient, these patients opted for conservative treatment.

CONCLUSION

Early age of presentation with men's predominance was noted in both groups. The IPSS-R score, which takes into consideration the karyotype, blast percentage, hemoglobin concentration, platelet, and ANC was more valid in determining the risk category for predicting the course of these patients than considering cytogenetic type alone. Furthermore, determining the coexisting genetic mutation by the Next Generation Sequencing method would help predict the clinical course more precisely. Hence, more cases involving the use of more modern molecular techniques need to be analyzed to validate our findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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