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Original Research Article

CLINICOHEMATOLOGICAL AND CYTOGENETIC PROFILE OF MYELODYSPLASTIC SYNDROMES WITH SPECIAL REFERENCE TO IDIOPATHIC CYTOPENIA OF UNDETERMINED SIGNIFICANCE AND IDIOPATHIC DYSPLASIA OF UNCERTAIN SIGNIFICANCE

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Abstract

Background: Myelodysplastic Syndromes (MDS) represent a heterogeneous group of clonal myeloid neoplasms characterized by peripheral cytopenias and bone marrow dysplasia [1]. Precursor states such as Idiopathic Cytopenia of Undetermined Significance (ICUS) [8] and Idiopathic Dysplasia of Uncertain Significance (IDUS) [10] remain completely unstudied in India.

Methods: A clinicohematological evaluation was conducted on 141 de novo MDS cases, 4 ICUS cases, and 23 IDUS cases at Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, between 2008 and 2016. Bone marrow aspiration, trephine biopsy, and G-banding cytogenetics were analyzed.

Results: Unlike Western data where the median age is around 65–76 years [3, 4], the median age in this Indian study was 28 years. Refractory Cytopenia with Multilineage Dysplasia (RCMD) was the predominant subtype (41.8%). Five IDUS patients (21.7%) demonstrated rapid progression to overt MDS during clinical monitoring.

Conclusion: MDS, ICUS, and IDUS manifest in a significantly younger demographic in the Indian subcontinent compared to Western populations, requiring rigorous diagnostic tracking.

Introduction

The myelodysplastic syndromes (MDS) are a very complex group of myeloid disorders characterized by peripheral blood cytopenias and morphologic evidence of dysplasia in bone marrow hematopoietic cellular elements [1]. Over the last decade, significant progress has been made in understanding molecular alterations, resulting in improved classifications, newer prognostic indices, and therapeutic modalities [1, 2].

Despite these advances, most patients with MDS eventually succumb either to disease-related cytopenic complications (such as severe infection or bleeding) or from transformation to acute myelogenous leukemia (AML) [1, 2]. Remarkably few clinical studies have been conducted on this disease spectrum in India [15]. This study presents 141 cases of primary Myelodysplastic Syndromes with special reference to their conceptual precursor borderlines: Idiopathic Cytopenia of Undetermined Significance (ICUS, 4 cases) [9] and Idiopathic Dysplasia of Unknown Significance (IDUS, 23 cases) [11].

To date, no systematic investigation has targeted ICUS and IDUS inside India, making this project an essential effort to shed light on these diagnostic interfaces.

Aims and Objectives

- To study the clinical and hematological profile of Myelodysplastic Syndrome.
- To study the clinical and hematological differences between adult & pediatric MDS.
- To attempt to study the histomorphological & cytogenetic profile of MDS cases wherever possible.
- To study & follow up “Idiopathic Cytopenia of Undetermined Significance” & “Idiopathic Dysplasia of Uncertain Significance”.

Material and Methods

Samples for bone marrow aspiration and core biopsy were collected from the Medicine and Pediatric departments of Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, between August 2008 and June 2016. Complete blood counts, peripheral smear analysis, and bone marrow processing were carried out using standard diagnostic methodologies. Bone marrow aspiration (BMA) smears were obtained via Salah's needles from the posterior superior iliac spine, air-dried, and stained with Leishman and Perl's Prussian blue methods to grade iron distribution [9]. Core trephine specimens (obtained via Jamshidi needles) were fixed in 10% natural buffered formalin, decalcified in 5% formic acid, and stained using Hematoxylin and Eosin (H&E) along with Reticulin staining for fiber indexing [9].

Cytogenetic microcultures of fresh bone marrow and peripheral blood cells were processed using standard RPMI 1640 medium, arrested with Colchicine, and evaluated via Trypsin-Giemsa G-banding according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines.

Results and Observations

Out of 141 primary MDS cases, pediatric individuals constituted 40 cases (28.36%) and adults represented 101 cases (71.64%). The general median age was 28.0 years (range 0.1–76 years), with pediatric and adult medians presenting at 10.0 and 38.0 years, respectively. The overall male-to-female ratio was 1.35:1.

Table 1: Distribution of MDS Subtypes by Gender and Cohort Groups

Subtype	Male	Female	Total	Pediatric	Adult	M:F Ratio
RA	0	3	3	0 (0.0%)	3 (3.0%)	—
RCMD	34	25	59	14 (35.0%)	45 (44.6%)	1.36:1
RAEB-1	15	11	26	4 (10.0%)	22 (21.8%)	1.36:1
RAEB-2	12	7	19	10 (25.0%)	9 (8.9%)	1.71:1
MDS-U	17	13	30	11 (27.5%)	19 (18.8%)	1.30:1
MDS del(5q)	1	0	1	0 (0.0%)	1 (1.0%)	—
MDS/MPN	2	1	3	1 (2.5%)	2 (2.0%)	2.00:1
Total Cohort	81	60	141	40 (100%)	101 (100%)	1.35:1

Table 2: Clinical Feature Prevalence: Pediatric vs. Adult Subpopulations

Clinical Symptom	Pediatric Cohort (n=22)	Adult Cohort (n=43)	p-value
Weakness	15 (68.2%)	43 (100.0%)	NS
Fever	16 (72.7%)	15 (34.9%)	0.004
Pallor	21 (95.5%)	42 (97.7%)	NS
Bleeding	5 (22.7%)	7 (16.3%)	NS
Hepatomegaly	8 (36.4%)	3 (7.0%)	0.01
Splenomegaly	8 (36.4%)	2 (4.7%)	0.003
Lymphadenopathy	4 (18.2%)	2 (4.7%)	NS

Table 3: Baseline Blood Count Groupings across MDS Subtypes

Laboratory Class	Total Cases (n=65)	RA	RCMD	RAEB-1	RAEB-2	MDS-U
Hb <3 g/dL	6 (9.2%)	0	2	0	4	0
Hb 3-6 g/dL	35 (53.8%)	2	14	9	5	3
Hb 6-10 g/dL	24 (36.9%)	1	10	2	4	5
TLC <4,000 /uL	36 (55.4%)	2	21	5	3	4
TLC 4k-12k /uL	17 (26.2%)	1	3	4	6	3
Plt <40,000 /uL	36 (55.4%)	3	16	7	6	3
Plt >80,000 /uL	19 (29.2%)	0	5	2	5	5

Table 4: Bone Marrow Structural and Lineage Dysplasia Profiling

Morphological Feature	Total Cohort (N=141)	RA	RCMD	RAEB-1	RAEB-2	MDS-U
Hypocellular	23 (16.3%)	1	11	2	1	8
Normocellular	67 (47.5%)	1	29	14	8	13
Hypercellular	39 (27.7%)	1	17	6	7	6
Dyserythropoiesis	93 (66.0%)	2	49	16	7	18
Dysgranulopoiesis	108 (76.6%)	0	49	19	11	27
Dysmegakaryopoiesis	56 (39.7%)	1	39	8	4	1

Cytogenetic findings

Cytogenetic analysis was done in total 5 cases. 3 cases showed positive cytogenetic findings. Cytogenetic examinations of 2 cases were unremarkable. The first case was a 72 years male diagnosed as RCMD who showed a deletion of long arm of 20 chromosome in 12% of cells. No other chromosomal abnormality was noted in this case. The second case was 25 years female diagnosed as RAEB-1 who showed

deletion of long arm of chromosome 7 in 25 % of cells with no other chromosomal abnormality. This patient later converted to Acute Myeloid leukemia 2 months after being diagnosed as RAEB-1.

The third patient was a 72 years male who showed characteristic monolobated megakaryocyte in bone marrow and in cytogenetic analysis showed deletion of long arm of chromosome 5. The patient did not deteriorate any further and showed good prognosis.

Table 5: Hematological parameters of ICUS cases

Sl. No.	Age	Sex	Hb (g/dl)	TLC (/uL)	ANC (/uL)	Plt (/uL)	Diagnosis	Follow up
1	21	F	8.2	650	300	178000	ICUS	Pt died after 9 days
2	45	F	7	4700	2200	428000	ICUS	ICUS
3	24	M	8.2	7500	2300	10000	ICUS	ICUS
4	44	M	8.1	3700	1200	60000	ICUS	ICUS

Four cases were diagnosed as ICUS. They all had persistent cytopenia for more than 6 months. There was no dysplasia in bone marrow.One patient died during the follow up, 9 days after doing bone marrow biopsy. Cause of death was unknown. Others had persistent cytopenia and did not progress to any other condition.

Table 5: Monitored Longitudinal Tracking and Dynamic Outgrowth of IDUS Cases

Patient ID	Hb (g/dL)	TLC (/uL)	Plt (/uL)	Marrow Dysplasia Subtype	Latency Phase	Overt MDS Transformation
1	10.5	4,500	300,000	Isolated Dysgranulopoiesis	4.0 Months	RCMD
2	11.0	5,500	425,000	Trilineage Dysplasia	6.0 Months	RCMD
3	10.9	7,500	255,000	Dyseryth + Dysgranulo	2.0 Months	RAEB-1
4	10.7	7,100	345,000	Dyseryth + Dysgranulo	2.5 Months	RAEB-1
5	10.6	8,100	452,000	Dysgranulo + Dysmegakaryo	1.0 Month	RAEB-2

23 cases were diagnosed as IDUS. The patients had minimal cytopenia and there was significant dysplasia in all cases. 2 patients progressed to RCMD while 2 patients progressed to RAEB-1. One patient progressed to RAEB-2. All the other patients did not progress further and remained in IDUS during the follow up.

Discussion

Epidemiological patterns compiled globally identify primary MDS as an elderly malignancy with a standard median age of 65 to 76 years [3, 4]. However, this cohort from northern India uncovers a dramatic shift towards young adults and pediatrics, featuring a collective median age of 28 years. This finding aligns with similar institutional records from eastern registries where presentation limits occur 1 to 2 decades earlier than Western registries [13, 14].

In this series, the most prevalent architectural variant was Refractory Cytopenia with Multilineage Dysplasia (RCMD), mirroring global shifts toward multi-lineage recognition over simpler unilineage pathways [5]. Cytogenetic tracking highlighted specific actionable

markers, such as a localized del(20q) in an elderly male, a predictive del(7q) deletion in a 25-year-old female with RAEB-1 who rapidly progressed to AML within 60 days, and a classic isolated del(5q) interstitial deletion corresponding to 5q- syndrome [6, 7].

Monitoring precursor configurations offers empirical validation for tracking borderline cytological pools, governed by the developmental intersection where ICUS + IDUS = MDS [10, 11].

The outcome of ICUS is variable. Some patients converted into MDS, some into AML and some died due to other reasons. In fair number of patients, the cause of death could not be ascertained. Some patients remained in ICUS and did not progress further.Thus, prediction of course of ICUS in difficult. A lot of work still needs to be done in this field which still remains largely unexplored. While ICUS variants feature persistent cytopenias without typical morphological alterations [8, 9], IDUS demonstrates notable bone marrow dysplasia alongside preserved cell boundaries [11, 12]. The dynamic decay of this equilibrium is evident in our longitudinal analysis, where 21.7% of IDUS borderlines transformed directly into explicit multi-lineage or high-grade blastic MDS subgroups [11]. This structural instability requires early diagnostics and proactive tracking before severe clinical complications develop [10, 14].

Conclusion

Myelodysplastic syndromes, ICUS, and IDUS are increasingly recognized among children and younger adults across India, diverging completely from traditional Western elderly epidemiological data where the disease predominantly manifests in the eighth decade of life [1, 15].

The prominent male preponderance observed across all diagnostic classes highlights potential regional environmental or occupational cofactor dynamics within the northern plains [1]. The outcome of ICUS is unpredictable. Crucially, the high, rapid rate of malignant transformation among monitored IDUS cases emphasizes its biological nature as an unstable, progressive pre-malignant clonal state rather than a benign architectural variant [11].

Because young adults represent the present economic backbone and children the societal future, the high disease burden found in these cohorts carries massive healthcare and social implications [1]. Developing standardized immunophenotypic screening panels, prioritizing routine core trephine biopsies alongside aspirations, and establishing regular cytogenetic surveillance networks are absolutely essential operational priorities to systematically intercept and manage bone marrow failure syndromes inside the Indian subcontinent [1, 11, 15].

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