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Myelodysplastic Syndromes in Jordan: a study form a large center

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ABSTRACT

Purpose: Study general data about myelodysplastic syndrome (MDS) and understanding the disease pattern in Jordan. **Patients And Methods:** A retrospective analysis was conducted on 134 patients, with MDS at King Hussein Medical Center, Amman, Jordan, From May2000 to May 2005 period. Recent World Health Organization (WHO) classification was applied. **Results:** Epidemiologic data showed male predominance as 84 of patients were males (63%) and 50 were females (37%), with a ratio of 1.7:1. The age of presentation ranged from 11 months to 90 years, with a mean of 63. 85% of the patients were older than 40 years. Refractory Cytopenia (RC) was the most common subtype (40%), followed by Refractory Anemia with Excess Blasts (RAEB) 38%. **Conclusion:** The incidence of MDS in Jordan might be higher than expected, and occur at relatively younger age groups.

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1. Introduction

The myelodysplastic syndromes (MDS) encompass a group of neoplastic hematopoietic disorders that affect predominantly the elderly, typically manifest paradoxically as peripheral blood cytopenia(s) despite bone marrow hypercellularity, and carry a variable probability of transformation into acute leukemia.¹ Many classification systems were made for MDS [1]. The incidence and prevalence of MDS in Jordan is unknown. We aim to study the pattern of MDS in a large medical institution in Jordan, with the application of the recent WHO classification.

2. Materials and Methods

King Hussein Medical Center (KHMC) is the largest multidisciplinary medical institution in Jordan dedicated to provide the utmost in patient care and professional training. It is a tertiary hospital with a current total capacity is 1000 beds. We retrieved the patients' records between May 2000 and May 2005; one hundred thirty four patients were diagnosed to have MDS. There were additional 14 cases which were not included due to inadequate specimens or clinical data. For every patient, the diagnosis was based on morphological examination of blood film, bone marrow aspirate and trephine biopsy. Cytogenetic study was

performed to all cases, while Immunophenotyping was limited to special cases. Besides, a thorough examination for blood count, serum vitamin B12, folic acid, lactate dehydrogenase (LDH) and ferritin is routinely done. Patients with dysmyelopoiesis secondary to vitamin B12 and folate deficiency were excluded. The French-American-British (FAB) Classification was originally applied to all cases, but for the sake of this study, we considered the recent WHO classification, too (Table-1).

3.Results

A total of 134 patients were reviewed. 84 of which were males (63%) and 50 were females (37%), with a ratio of 1.7:1. The age of presentation ranged from 11 months to 90 years, with a mean of 63. 85% of the patients were older than 40 years.

Symptomatic anemia (pallor, fatigue) was the leading complaint, occurred in 66% of patients. Other signs and symptoms are: splenomegaly (17%), mucocutaneous bleeding (14%), lymphadenopathy (10%), constitutional symptoms (10%), asymptomatic and incidental findings (5%).

Peripheral cytopenia(s) was evident in all patients. Thrombocytopenia (platelets count < 150*10⁹ \ L) was present in 75% of patients. 50% of patients had low packed cell volume (<15-25%) at the time of presentation. While leucopenia (WBC count < 4*10⁹ \ L) was seen in 25% patients. Bone marrow aspirates were available for all patients. Hypercellular marrow was noted in 78% of patients, while 12% had hypocellular marrow and 10% had normocellular marrow.

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Table-1: WHO Classification of Myelodysplastic syndrome, 2008

RCUD	
RA	Anemia (Hb<10 g/dL); _ neutropenia or thrombocytopenia; <1% circulating blasts; <5% medullary blasts; unequivocal dyserythropoiesis in ≥10% erythroid precursors; dysgranulopoiesis and dysmegakaryopoiesis, if present, in ≤10% nucleated cells; <15% RS; no Auer rods
RN	Neutropenia (absolute neutrophil count <1.8 _ 10 ⁹ /L); _ anemia or thrombocytopenia; <1% circulating blasts; <5% medullary blasts; ≥10% dysplastic neutrophils; ≤10% dyserythropoiesis and dysmegakaryopoiesis; <15% RS; no Auer rods
RT	Thrombocytopenia (platelet count <100 _ 10 ⁹ /L); _ anemia or neutropenia; <1% circulating blasts; <5% medullary blasts; ≥10% dysplastic megakaryocytes of ≥30 megakaryocytes; ≤10% dyserythropoiesis and dysgranulopoiesis; <15% RS; no Auer rods
RARS	Anemia; no circulating blasts; <5% medullary blasts; dyserythropoiesis only, with RS among >15% of 100 erythroid precursors; no Auer rods
RCMD	Cytopenia(s); <1 _ 10 ⁹ /L circulating monocytes; <1% circulating blasts; <5% medullary blasts; dysplasia among >10% cells of ≥2 lineages; no Auer rods
RAEB-1	Cytopenia(s); <1 _ 10 ⁹ /L circulating monocytes; <5% circulating blasts; 5%–9% medullary blasts; dysplasia involving ≥1 lineage(s); no Auer rods
RAEB-2	Cytopenia(s); <1 _ 10 ⁹ /L circulating monocytes; 5%–19% circulating blasts; 10%–19% medullary blasts; dysplasia involving ≥1 lineage(s); _ Auer rods
RAEB-F	Similar to RAEB-1 or RAEB-2, with at least bilineage dysplasia and with diffuse coarse reticulin fibrosis, with or without collagenous fibrosis
MDS-U	Pancytopenia; <1 _ 10 ⁹ /L circulating monocytes; %1% circulating blasts; <5% circulating blasts; dysplasia in <10% cells of ≥1 lineage(s); demonstration of MDS-associated chromosomal abnormality(ies), exclusive of 18, del(20q), and -Y
MDS-isolated del(5q)	Anemia; platelet count may be normal or increased; <1% circulating blasts; <5%, medullary blasts; megakaryocytes with characteristic nuclear hypolobulation; isolated del(5q) cytogenetic abnormality involving bands q31-q33
RCC	Thrombocytopenia, anemia, and/or neutropenia; <2% circulating blasts; <5% medullary blasts; unequivocal dysplasia in ≥2 lineages, or in >10% cells of one lineage; no RS

Abbreviations: RCUD; refractory cytopenias with unilineage dysplasia, RA; Refractory Anemia, RN; Refractory Neutropenia, RT; Refractory Thrombocytopenia, RARS; Refractory Anemia with Ring Sideroblasts, RS; Ring Sideroblasts, RCMD; Refractory Cytopenias with Multilineage Dysplasia, RAEB; Refractory Anemia with Excess Blasts, RAEB-F; Refractory Anemia with Excess Blasts with Fibrosis, MDS-U; Myelodysplastic Syndrome-unclassifiable, RCC; Refractory Cytopenia of Childhood.

91% of patients were considered primary MDS and classified into one of the groups according to the FAB classification. The remaining cases were secondary MDS; 7% had prior chemotherapy with alkylating agents and 2% had concurrent infectious disease (tuberculosis, viral infection). We reviewed the cases of primary MDS and applied the latest WHO classification for them.

Refractory Cytopenia (RC) was the most common subtype (40%), followed by Refractory Anemia with Excess Blasts 1,2 (RAEB-1,2) (38%), then Refractory Anemia with Ring Sideroblasts (RARS) (12%). Next was Chronic Myelomonogenous Leukemia (CMML) (6%), then 5q del (2%), and the last was Refractory Cytopenia of Childhood (RCC) (1%) (Table-2). Within RC, Refractory Cytopenia with multilineage dysplasia (mostly anemia with thrombocytopenia) was the most common finding (45% of RC cases). Refractory Anemia (RA) formed 40%, and the rest was Refractory Thrombocytopenia (RT). No cases of Refractory Neutropenia were encountered. Secondary MDS were not include in the classification.

Regarding the outcome, 40% of patients with RAEB and CMML developed leukemic transformation, which occurred from one to eight months after diagnosis. Patients with RC and RCC had a survival rate of around 5 years, while patients with RARS survived around 3 years. Isolated del (5q) syndrome had the best survival, which surpassed 20 years.

Table-2: The pattern of MDS in KHMC

Subtype	Percentage of cases
RC	40%
RARS	12%
RAEB1,2	38%
MDS-isolated del (5q)	2%
RCC	1%
CMML	6%

4. Discussion

MDS is a bone marrow clonal stem cell disorder resulting in disorderly and ineffective hematopoiesis manifested by irreversible quantitative and qualitative defects in hematopoietic cells. The disease results from clonal expansion of the multipotential hematopoietic cell with an increased apoptosis of blood cells precursors [3].

The estimated annual incidence of MDS is about 3.5–10 per 100,000 in the general population [4], which rises to 45 per 100,000 for people over the age of 70.5 The median age of onset is between 60 and 70 years [4]. In children, the incidence is 0.5–4/100,000 and most cases occur at the age 6–8 [6,7]. Little is known about the prevalence of MDS in Jordan or Arabic populations, as the Jordanian population is dominantly young [8], and the National Cancer Registry in Jordan does not include MDS within cancer diseases. This is the second study of its kind in Jordan that shows a relatively younger age of onset of MDS in the population [8].

Famous to its heterogeneous types, the etiology of MDS is complex. Environmental exposure to ammonia, agricultural chemicals, solvents (benzene) and smoking are associated with MDS. The mostly studied chemical, benzene, is metabolized to hydroquinone which causes damage to hematopoietic progenitor cells and induces MDS and leukemia [9]. Genetic risk factors for MDS are: family history of hematological malignancy [10], Fanconi anemia, dyskeratosis congenita, Shwachmann-Diamond and Diamond-Blackfan syndromes [12]. People with polymorphism in the genes responsible for coding detoxifying enzymes for potential carcinogens are at increased risk for MDS [13]. Therefore, chronic exposure to high phenol, present in coffee, fruit and vegetables, leads to accumulation of hydroquinone in the body and predisposes to the development of MDS in susceptible patients [14]. MDS can arise as a late complication of chemo or radiotherapy, known as secondary MDS [12]. In our study, around 70% of the patients are smokers, 10% had a confirmed history of exposure to agricultural chemicals, while a family history of hematological malignancies was difficult to know.

Chromosomal abnormalities occurred in almost half cases of primary MDS and 95% of secondary MDS. Most chromosomal defects in MDS are nonspecific, with the exception of 5q del [15]. Chromosomal deletions are the most common defects in both primary and secondary MDS. Deletions are generally interstitial, rather than terminal. Deletions observed along with other chromosomal abnormalities are associated with a more advanced disease [16]. Cytogenetic alteration has a prognostic impact. In our study, the entire 134 patients had chromosomal abnormalities. More than 50% had chromosomal deletions, and 37% had abnormal karyotype. However, complex cytogenetic aberrations and chromosome translocations were frequently observed and related to poor prognosis. Both multiple chromosomal deletions and translocations were detected in RAEB cases.

The survival rate is consistent with what is reported in the literature. The best survival was for cases of Isolated 5q del, while the shortest was for cases of RAEB. We did not include the modality of treatment and its effect on survival in this study, but in a previous study from Jordan, survival was shorter for patients who received blood transfusion [8].

5. Conclusion

We conclude that the incidence of MDS in Jordan might be higher than expected, and occur at relatively younger age groups. The pattern of MDS subtypes are close to that reported in the literature, with a lower incidence of Isolated 5q del syndrome. Chromosomal abnormalities are common, and will be very helpful in establishing the diagnosis in suspected cases, especially in the young. We believe that there is an impending need to make a population based study about the incidence and prevalence of the disease in Jordan, which would possibly show a relatively higher rate than expected.

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