ORIGINAL ARTICLE

Clinicopathological Analysis of Myelodysplastic Syndrome According to French-American-British Classification

Ayesha Ehsan, Mona Aziz, Sarah Arif, Muhammad Javed Asif, Tooba Ammar and Shahida Amjad Riaz Shah

ABSTRACT

Objective: To evaluate the age of onset, gender ratio, clinical presentation of Myelodysplastic syndrome patients, and to classify these patients according to French-American-British classification on the basis of morphological features in blood and bone marrow.

Study Design: A case series.

Place and Duration of Study: The Department of Haematology, Shaikh Zayed Hospital, Lahore, from April 2004 to March, 2007.

Methodology: Fifty patients of primary Myelodysplastic syndrome (MDS) were studied. The patients were classified according to French-American-British (FAB) criteria and the epidemiological, clinical and haematological features of MDS patients were evaluated. Descriptive statistics were used to describe data.

Results: There were 31 males and 19 females. The mean age was 41 years. According to FAB classification, 39 cases of refractory anaemia, 1 case of refractory anaemia with ring sideroblast, 6 cases of refractory anaemia with excess of blasts and 4 cases of refractory anaemia with excess of blasts in transformation were identified. The commonest complaint was easy fatiguability affecting 41 cases (82%). Anaemia was the most common finding seen in 47 patients (94%). Pancytopenia was seen in 33 cases (66%). Dyserythropoeisis was present in 42 (84%); dysmyelopoeisis was seen in 21 (42%) and morphologically abnormal megakaryocytes were identified in 29 (58%) of the bone marrow aspirates. Grade-III reticulosis was seen in 9 bone marrow trephine biopsies. Abnormal localization of immature precursors (ALIP) were present in 18 cases.

Conclusion: MDS was more frequent in young males. Refractory anaemia constituted a major chunk of the disease entity.

Key words: *Myelodysplastic syndrome. FAB classification. Dyserthyropoiesis. Megakaryocytosis. Refractory anaemia.*

INTRODUCTION

The Myelodysplastic syndromes (MDS) are a group of clonal haemopoietic stem cell diseases characterized by dysplasia and ineffective haematopoiesis in one or more of the three major myeloid cell lines.[1] The natural history of MDS varies widely; ranging from chronic anaemia with low propensity for leukaemic conversion to disorder characterized by profound disturbance in haemato-poeisis and high risk of 10-40% to progression and to acute myeloid leukaemia.[2]

The French-American-British (FAB) group classification is based on blast count, ring sideroblasts, number of monocytes in peripheral blood and Auer rods in 1982. It divides MDS into 5 sub-groups with significantly different prognosis; these include refractory anaemia (RA), refractory anaemia with ring sideroblasts (RARS), refractory anaemia with excess of blasts (RAEB) refractory anaemia with excess of blasts in transformation (RAEB-t) and chronic myelomonocytic leukaemia.

Department of Haematology, Sheikh Zayed Postgraduate Medical Institute, Lahore.

Correspondence: *Dr. Ayesha Ehsan, 892 Shadman I, Lahore. E-mail: ayesha_4@hotmail.com*

Received September 09, 2008; accepted March 31, 2010.

In 1999 World Health Organization (WHO) published a new classification of MDS which was further revised in 2008. It took into account the additional information regarding prognosis and cytogenetic analysis.

Both these classifications are currently in use however, the classification of myelodysplastic syndrome is a continuously evolving process.[3,4]

The incidence of these syndromes is about 5 per 100,000 persons per year in the general population, but it increases to 20-50 per 100,000 persons per year after the age of 60 years.[5] Therefore, the suggested treatment protocols are designed for elderly population predo-minantly.[6]

In the paediatric haematological malignancies, inter-nationally, MDS represents 1.1-8.7% with an annual incidence of 0.5-4 per million.[7,8] A single centered study at Shaikh Zayed Hospital, Lahore, reported MDS to be 4.6% of all haematological malignancies in patients less than 15 years old.[9]

In Pakistan, a few epidemiological studies that were carried out showed male preponderance, a younger age of onset and relatively higher frequency of aggressive disease, as compared to American and European statistics.[9-13] This study was conducted to elaborate the epidemiological and clinicopathological features of MDS patients in Pakistan, to assess the applicability of FAB

classification on a group of Pakistani MDS patients and compare the findings with other regional and international reports.

METHODOLOGY

This observational study was carried out at the Department of Haematology, Shaikh Zayed Hospital (SZH) Lahore, from April 2004 to March 2007. All the patients visiting Shaikh Zayed Medical Complex during the study period were included in the study by non-probability purposive sampling. Fifty patients were found to fulfill the diagnostic criteria for MDS during this time period. Patients who were suffering from deficiencies of iron, vitamin B_{12} and folic acid; and those cases diagnosed with chronic infections i.e. tuberculosis, leprosy, typhoid, chronic active hepatitis and AIDS or chronic inflammations i.e. rheumatoid arthritis, systemic lupus erythematosus were exclude. A detailed history was taken about residence near factory area, occupation and exposure to toxins, fever; weight loss (about 10% in the last 6 months); bleeding from any site including multiple bruises with minor trauma, purpura, epistaxis, gum bleed, hematemesis, haemoptysis, haematochezia, malaena, haematuria, manorrhagia, excessive bleeding from wounds or cuts or after a surgical procedure; breathlessness on mild exertion and easy fatigability. General physical examination including pallor fever, bleeding manifestations in the skin (e.g. bruises and purpura), signs of bleeding from the nose, oral cavity, vagina, anal canal; accessible lymph adenopathy in the cervical, axillary and inguinal region. Hepatomegaly and splenomegaly were sought in abdominal examination and confirmed by abdominal ultrasound.

Venous blood samples (2 ml) were taken and tested in Sysmex KX 21 for complete blood counts (CBC). Blood films were stained by May-Grunwald-Giemsa stain and peripheral smear was examined. Bone marrow aspirates were done from right posterior iliac crest. May-Grunwald-Giemsa staining was performed on the aspirate which was then examined for evidence of dysplasia, erythropoiesis, myelopoiesis and megakaryopoiesis. Blast percentage of non-erythroid nucleated bone marrow cells was calculated from a myelogram of 500 cells.[3,6] The blast cells were confirmed as myeloid blasts by staining with myeloperoxidase. Non-specific esterase staining was done for confirming blasts for monocytic lineage. Perl staining was done on patient's bone marrow aspirate slides for ring sideroblasts. Bone marrow trephine biopsies were stained by haematoxylin and eosin. Cellularity assessment was based on visual examination and graded into three groups; normocellular (30-50% of intertrabecular spaces occupied by haematopoeitic cells), hypercellular (> 50%), hypocellular (< 30%).[6] Abnormal localization of immature precursors (ALIP) were also sought. Silver impregnation was carried out to grade reticulosis from 0 to 4 depending on severity. The data was used to classify patients of MDS.

The collected data was analysed by using SPSS version 10.0. Nominal data of variables including pallor, fever, bleeding, weight loss, splenomegaly, hepatomegaly, lymphadenopathy; and bone marrow features including cellularity, erythropoiesis, myelopoeisis, megakaryopoiesis and ALIP were recorded as frequency/ percentages. The cohort was divided into 2 groups on the basis of age above and below 14 years. The mean age of the paediatric group and the adult group was calculated separately. The variables in CBC including haemoglobin (Hb), TLC, platelet count and mean cell volume were recorded as mean ± standard deviation for each group.

RESULTS

Fifty patients of primary MDS were studied. There were 31 males and 19 females. There were 6 cases below 14 years of age and the rest were above 14 years. The age ranged from 2 to 81 years. There was a predominance of adults. The mean age for the whole cohort was 41 years. However, the adult cases had a mean age of 45.34 years and the paediatric age group had a mean age of 9.1 years. The mean age of patients with RA was 43.6 years. Patients with RAEB and RAEB-t were markedly younger than other FAB types with a mean age of 38 and 17 years respectively.

According to FAB classification 39 cases of RA, 1 case of RARS, 6 cases of RAEB, 4 cases of RAEB-t were identified. RA represented 78% of the cases and constituted the predominant cohort population.

The commonest complaint of the patients was pallor and easy fatiguability effecting 41 cases (82%). Fever 26 (52%) was the next most common symptom followed by bleeding 19 (32%), hepatomegaly 3 (6%), splenomegaly 6 (12%), lymphadenopathy 8 (16%) and weight loss 5 (10%) were relatively rare the latter found in 3 patients of RAEB and 2 of RAEB-t.

Anaemia was the most common finding seen in 47 patients (94%). Hb was less than 8 g/dl in 39 (78%) patients. Only 2 patients had Hb above 12 g/dl at presentation. Pancytopenia was the most common presentation seen in 33 cases (66%). Bicytopenia was seen in 12 (24%) patients. The combination of anaemia and thrombocytopenia was seen in 6 (12%) patients; anaemia with leucopenia was seen in 4 (8%) patients and the combination of thrombocytopenia and leucopenia was seen in 2 (4%) patients. Anaemia was the sole presentation in 4 (8%) patients. Only one (2%) patient presented with isolated thrombocytopenia. Peripheral smear revealed dimorphic red cell morphology consisting of either normochromic normocytic mixed with macrocytes or hypochromic microcytic RBCs mixed with a large number of macrocytes. Macrocytosis was a

Table I: Distribution of haemoglobin, total leucocyte count, platelet count and mean cell volume in 50 cases of MDS.

Parameter observed	Paeds (Mean ± Standard dev.)	Adults (Mean ± Standard dev.)
Haemoglobin (gram/decilitre)	6.4 ± 2.7	6.5 ± 2.7
Total leucocyte count (x10^9 per-litre)	11.1 ± 12.3	3.6 ± 3.3
Platelet count (x10^9 per litre)	47.0 ± 57.5	57.9 ± 74.6
Mean cell volume (femtolitre)	95.2 ± 9.3	95.9 ± 10.3

Table II: Comparison of percentage distribution of MDS categories classified by French-American-British classification (figures express percentage of cases).[24]

Country	Jap	Pak	Aust	Arg	Sing	Ind	Pak
Ref No.	20	9	22	23	21	18	This study
Year	1995	1998	2001	2002	2004	2005	2010
RA	40	28	33	46	58.1	64	78
RARS	10	17	11	9	14	5	2
RAEB	33.9	40	21	23	16.3	22	12
RAEB-t	10	9	12	11	7	5	8
CMML	6.1	6	23	11	4.6	4	0

RA= Refractory anaemia; RARS= Refractory anaemia with ring sideroblasts; RAEB= Refractory anaemia with excess of blasts; RAEB-t= Refractory anaemia with excess of blasts in transformation; CMML= Chronic myelomonocytic leukemia. Aus= Austria; Arg= Argentina; Sing= Singapore; Jap= Japan; Ind= India; Pak= Pakistan. Ref. No.= Reference number; Year= Year of publication.

consistent feature in RA and RARS (80%), RAEB showed main population of normochromic normocytes and a minor population of hypochromic microcytes (12%), RAEB-t presented with a major population of hypochromic microcytes (8%). Mean Cell Volume (MCV) was increased in 15 (30%) patients. It was 97.0 and 98.5 for low grade diseases (RA and RARS); it was 91.3 and 90.6 for high grade categories (RAEB and RAEB-t). Pseudo Pelger neutrophils were present in 39 (78%) cases.

Bone marrow trephine biopsy was found to be hypercellular in 31 (62%) cases, normocellular in 11 (22%) and hypocellular in 8 (16%) cases. Bone marrow aspirate showed evidence of dyshaematopoiesis in atleast one cell line in all patients. Dyserythropoeisis was present in 42 (84%) of aspirates. Dysmyelopoeisis was seen in 21 (42%) of aspirates and morphologically abnormal megakaryocytes were identified in 29 (58%) of the aspirates. Dyserythropoiesis affected 36 cases of RA; one case of RARS and 4 cases of RAEB. Dysplasia in one cell line was seen in 23 (46%) cases, bi-lineage dysplasia was seen in 16 (32%) cases and tri-lineage dysplasia was present in 11 (22%) cases. Erythroid hyperplasia was present in 32 (64%) of aspirates. Myeloid hyperplasia was seen in 19 (38%) cases and 15 (30%) cases showed increased megakaryocytes.

Dysmegakaryopoiesis was confirmed in trephine biopsies and micromegakaryocytes were seen in 50% of the biopsies. Hypercellularity and dysplasia being a characteristic feature of MDS were present in a very high proportion of cases.

Grade-III reticulosis was seen in 9 cases (7 cases of RA, 2 cases of RAEB and 2 cases of RAEB-t). In the adult group, grade-III reticulin was present in 7 of 44 (15.9%) cases. In the paediatric group, reticulin was grade-III in one third of the cases i.e. 2 of 6 (33%) patients. Abnormal localization of immature precursors (ALIP) was present in 4 cases of RAEB, one case of RAEB-t and 9 cases of RA.

The occupation history revealed; 17 students, 13 home makers, 8 farmers, 9 office workers/shopkeepers, 2 workers of leather tanning industry and 1 worker of automobile workshop. Insecticide's exposure was reported by 5 farmers, chemical exposure was reported by the leather and automobile workshop workers. The rest of the patients did not give history of exposure to carcinogenic chemicals. Three patients gave history of residence near factory area.

DISCUSSION

Most published data on myelodysplastic syndromes (MDS) is derived from Western countries, which report MDS as a disease of the elderly. This study consisted of 50 patients belonging to Pakistan. The mean age of the adult cohort was 45.34 years. This is similar to studies from India which reported the median age of 45 and 55 years and from China, which reported a mean age of 49 years and 50 years.[14-17] This is in wide contrast to European studies, which estimate the mean age at diagnosis, to be above 70 years and from Singapore which is 64 years.[18,20,21] The studies based on South-East-Asian population including Pakistan, India, China showed a much younger age of onset, as compared to European studies. This finding re-affirms that the median age of onset of MDS is in the fourth decade in South East Asian population. Other Asian studies, have observed younger age for aggressive disease categories.[16] The mean age of RA in the studied group to be 7 years older than mean age for RAEB and the mean age for RAEB-t to be half that of RAEB.

The male to female ratio of 1.63:1 in this study compared well with 1.8:1 reported from India, from Singapore as 1.5:1 and from Japan as 1.7:1.[14,15,19,20] The sex ratios suggest that MDS affects more males than females in Asia, while it afflicts both genders almost equally 1:1.05 in Europe.[13]

Pallor and easy fatigueability has been considered the most common complaint of MDS in many other studies,[10,16,20] followed in frequency by bleeding and infections as found in this study.

In the adult group, grade-III reticulin was present in only a few patients, however, in the paediatric group reticulin was grade-III in one third of the patients. The frequency of reticulosis in paediatric MDS is reported to be relatively higher than that in adults by Badar *et al.*[22] This study gave a similar result. ALIP are considered independent prognostic markers in MDS and their presence is helpful in the diagnosis as they are an indicator for abnormal growth pattern.[3] RA was found as predominant disease category in the relatively recent studies from India, Japan, Singapore and Pakistan.[14,19,20,23]

It may be a result of the increased awareness of RA in the recent years. RAEB had previously been reported as the predominant disease category in studies carried out in the 1990s.[10] The second most common sub-category was RAEB in nearly all the recent reports followed in frequency by RAEB-t. RARS and CMML have been reported to be relatively uncommon entities in local literature;[9,12,13,15] similar results were obtained in this study.

CONCLUSION

In this setting, MDS was seen in young age group. MDS affected more males than females. RA constituted a major chunk of the disease entity. Our results were comparable to regional studies. Further, large multi-centre studies with cytogenetic evaluation and follow-up are required to collect additional information of the spectrum of MDS in Pakistani population. It is also suggested, that further studies be under-taken to form proposals for improving treatment protocols for young patients with RA, who form a bulk of the diseased population in Pakistan.

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