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(Received September 29th, 2009. Revised December 7th 2009, Accepted January 4th 2010. Published *Online* January 11th, 2010.)

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Myelodysplastic Syndrome: Features and Profiles of case series at Advanced Medical and Dental Institute (AMDI)

The purpose of this study was to obtain the profiles and clinical features of a clonal disorder of pluripotent stem cells of bone marrow known as Myelodysplastic Syndrome (MDS). Eight cases of probable MDS were reviewed at Hospital Kepala Batas/Advanced Medical and Dental Institute from November 2003 to December 2007. Peripheral blood film (PBF) and bone marrow examination were performed for diagnosis, however cytogenetic studies were excluded for diagnostic confirmation due to lack of facility at the centre. Moreover, majority of the patients refused bone marrow examination. Three cases were male and five cases were female. Mean age at presentation was 70 years old -ranging from 61 to 75 years old. Majority of patients presented with symptoms of anaemia. Only two patients were confirmed as MDS through bone marrow study, whilst six others were treated as presumed MDS. Five patients, among eight, refused bone marrow aspiration and trephine biopsy (BMAT) and one patient refused second BMAT procedure because of first BMAT was inconclusive. Other possible diagnostic possibilities for cytopenia were ruled out by history and clinical examination. While the series described interesting clinical features at the local centre, diagnostic confirmation remains a problem in our setting because of lack of bone marrow examination. It is worth to note that bone marrow examination is least acceptable to most patients in many cultures. These cases lead towards more vigilant efforts to diagnose and maintain high index of suspicion in cases of cytopenias in elderly population for diagnosis of MDS.

Key words: Myelodysplastic syndrome, Bone marrow, Anemia.

INTRODUCTION

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of closely related clonal hematopoietic disorders. All such disorders are characterized by hypercellular or hypocellular marrow with impaired morphology and maturation (dysmyelopoiesis) and peripheral blood cytopenias, resulting from ineffective blood cell production. In myeloid hematopoiesis, all three cell lineages including erythrocytic, granulocytic, and megakaryocytic are involved. Although clonal, myelodysplastic syndrome (MDS) is considered a premalignant condition in a subgroup of patients who often progress to acute myeloid leukaemia (AML) when additional genetic abnormalities are acquired {1}. MDS can be classified under guidelines of WHO as follows {2}

WHO Classification of MDS

The pathogenesis of MDS is unclear but is presumed to start following genetic damage to a multipotent haemopoietic progenitor cell. This leads to increased stem cell proliferation but ineffective differentiation and maturation, leading to the paradox of a hypercellular bone marrow but a pancytopenia in peripheral blood. A high rate of apoptosis is present in bone marrow precursors {1, 3}. The disease has an incidence of 4 in 100, 000 and male predominance is high. Majority of patients are above 70 years but patients less than 50 years old have also been reported. The evolution is slow and the disease is noticed by chance when a patient has a blood count checked for some unrelated reasons. The symptoms, if present, are those of anemia, infections or of easy bruising or bleeding. In some patients transfusion-dependent anemia dominates the course, while in others recurring infection or spontaneous bruising and bleeding are the major clinical problems. Because the

Disease	Blood	Bone Marrow
Refractory anemia (RA)	Anemia; no or rare blasts	Erythroid dysplasia; <5% blasts; <15% RA ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias; no or rare blasts; no Auer rods; <1 × 109/L monocytes	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines; <5% blasts; no Auer rods; <15% ringed sideroblasts
Refractory anemia with ringedsideroblasts (RARS)	Anemia; no blasts	Erthroid dysplasia;<5% blasts; ≥15% ringed sideroblasts
RCMD-RS	Cytopenias; no or rare blasts; no Auer rods; <1 ×109/L monocytes	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines; <5% blasts; no Auer rods;<15% ringed sideroblasts
RAEB-1	Cytopenias; <5% blasts; no Auer rods; <1 × 109/L monocytes	Unilineage or multilineage dysplasia; 5%-9% blasts; no Auer rods

RAEB-2	Cytopenias; 5%-19% blasts; Auer rods ±; <1 × 109/L monocytes	Unilineage dysplasia in granulocytes or megakaryocytes; <5% blasts; no Auer rods
MDS-U	Cytopenias; no or rare blasts; no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes; <5% blasts; no Auer rods
MDS w/del(5q)	Anemia; <5% blasts; platelets normal or increased	Normal to increased megakaryocytes w/ hypolobated nuclei; <5% blasts; no Aeurrods; isolated del(5q)

MDS-U: unclassified MDS; RCMD: refractory cytopenia with multilineage dysplasia; RCMD-RS: RCMD and ringed sideroblasts

neutrophils, monocytes and platelet are often functionally impaired, spontaneous infections in some cases or bruising or bleeding in others may occur out of proportion to the severity of the cytopenia. The spleen usually remains normal on palpation {3}.Cytogenetic abnormalities are more frequent in secondary MDS than the primary one, and mostly constitute partial or total loss of chromosomes 5 or 7 or trisomy 8. The loss of chromosomes 5 bands q13 to q33 in elderly females with macrocytic anaemia, normal or raised platelet counts in the presence of micromegakarocytes are termed the 5q-syndrome and have good prognosis. RAS oncogenes (usually N-RAS) mutations occur in about 20% of cases and mutations of FMS in approximately fifteen percent {3}. Treatment is often difficult because chemotherapy rarely cures the disease and intensive or even low dose chemotherapy may in some cases make the situation worse. The treatment is divided into two groups that is low risk MDS and high risk MDS. Low risk MDS is defined as less than 5% blast in the marrow and only one cytopenia and favorable cytogenetics. Low risk MDS usually managed conservatively with red blood cell transfusion, platelet transfusion and antibiotics as required. Attempts may be made to improve marrow functions with haemopoetic growth factors, either singly or in combination. Erythropoeitin (EPO) benefits in many cases of refractory anaemia. Granulocyte colony-stimulating factor (G-CSF) shows synergy with EPO and may increase the response rate. Cyclosporine or anti-lymphocyte globulins (ALG) occasionally improve patients, particularly those with a hypocellular bone marrow. In the long term, iron overload may be a problem with massive transfusion. Other agents (e.g. Thalidomide or its derivatives Lenalidomide) may be of benefit, especially in the 5q-syndrome. In selected patients, standard or low intensity allogenic transplantation offers a permanent cure. In high risk MDS, with 5% or more blasts in the marrow and often unfavorable cytogenetic and pancytopaenia, a variety of treatment options are attempted to improve the overall prognosis with various degrees of success. The treatment extends from general support alone to intensive chemotherapy. Fewer patients in the high risk group with anemia are helped by recombinant EPO, even with the addition of G-CSF, than in the low-risk group. Single agent chemotheraphy such as hydroxyurea, etoposide, mercaptopurine or low dose cytosine arabinoside may be given with some benefit to patients with refractory anemia with excess blasts (RAEB). The demethylating agents' i.e. 5' azacytidine or decitabine have been of benefit to approximately 60% of trials patient. Chemotheraphy as given in AML may be tried in high risk patients. Stem cell transplantation (SCT), the prospect of complete cure for MDS and the advent of non- myeloablative conditioning is increasing the age range of patients that may be treated.

METHODOLOGY

This case series was studied at Hospital Kepala Batas (HKB)/AMDI, Pulau Pinang from November 2003 to December 2007. Peripheral Blood Film (PBF) examination performed within this period of study were traced from the Pathology Department, HKB and reviewed. There were a total of 3804 PBFs performed within this period. Subsequently, those cases were selected which were reported as bicytopenia or pancytopenia. Upon tracing the case notes, eight patients were identified who were treated as possible MDS. Their files' Notes including detailed history and examination were found but lacked autoimmune workup including toxins and radiation. However, only 2 patients were confirmed as MDS from bone marrow study. All the collected data were analyzed using Microsoft Excel 2007.

RESULTS

From November 2003 to December 2007, eight cases of cytopenia presumed as MDS were found. Out of the eight cases, only two were confirmed as MDS by bone marrow examination. The mean age of the patients was 70 years ranging from 61 – 75 years old. Three were female patients of Malay race. Seven patients presented the symptoms of anemia i.e., lethargy in five cases and shortness of breath in two cases. One patient had atypical presentation of chronic constipation. None of the patient presented with symptoms of bleeding tendencies or infection. Only one patient had prior blood transfusion. Two patients were on ischemic heart disease medication. None received chemotherapy or radiotherapy. Pallor was present in all (100%) of the patients and presence of petechiae in 12.5%. Splenomegaly was absent in all patients. Other findings included hepatomegaly and cardiac murmur. **Table I** shows the clinical features of these cases. Pancytopenia and bicytopenia were 63% and 37% of the patients respectively. 25% of the patients had blast cells. Monocytosis and reticulocytosis were absent in all the patients. Three patients gave their consents for bone marrow aspiration and trephine biopsy but one of the results was inconclusive. Two patients had hypercellular marrow despite pancytopenia, dyserythropoiesis and presence of granulocyte precursors. One had abnormal megakaryocytes whilst none had ring sideroblast. **Table II** describes the laboratory findings of the cases. All of them received (100%) red cell transfusion and half of them received platelet transfusion. Antibiotic therapy was given in 25% of cases while 12.5% were supported with EPO. Four patients are still under regular follow up, one patient has defaulted treatment. **Table III** and **figure 3** show the management and outcomes of these patients. **Figure 1** and

2 demonstrate the demographic descriptions and picture 1 – 6 show the examples of the PBF findings in these patients.

DISCUSSION

Incidence of MDS is four in 100,000 with male predominance at above 50 years of age. The disorder may appear in childhood after 2 years age. Most cases occur between ages of 50 and 90 years; with males affected 1.5 more likely than females {3}. However, in our study, most cases were in the age group of 50 to 70 years, with female preponderance (1.7:1). The evolution is often slow. Patients may be asymptomatic and if symptoms present, are those of anaemia (pallor, weakness, loss of well-being, exertional dyspnoea), infections related to granulocytopenia or haemorrhage related to thrombocytopenia at the time of diagnosis (3, 4). Hepatomegaly or splenomegaly occurs in approximately 5 to 10 percent of patients, respectively {5}. In our study seven out of 8 patients presented with symptoms of anaemia, mostly lethargy and shortness of breathe ((five and two patients respectively in this study). However one patient presented with chronic constipation and abdominal pain. None came with symptoms of infection or bleeding. Only 1 patient presented with hepatomegaly and confirmed by ultrasonography scan.MDS in the peripheral blood may be evident by pancytopenia (30-50%), while 20% have anaemia in combination with either neutropenia or thrombocytopenia . In our study, 100 % of the patients presented with pancytopenia.The ability to diagnose MDS is critically dependent on optimum staining of blood and marrow slides with a Romanowsky stain. The main morphological abnormalities found in MDS are as follows {6}. Morphological abnormalities in red cells are oval macrocytosis, anisopoikilocytosis, hyperchromic red cell fragments, basophilic stippling and/or nucleated red cells. Most of the above features were present in the FBPs in our study but none had basophilic stippling. Morphological abnormalities in leucocytes are hypogranular neutrophils, hypo lobular neutrophil nuclei (Pelger cells) and/or coarse nuclear chromatin clumping. Five out of eight (62.5%) cases showed dysplastic looking neutrophils corresponding with the above statement. Morphological abnormalities in platelets are giant platelets and/or agranular platelets. Only two out of eight FBPs in our series had giant platelets while others had low count with no clumping seen. In BMA, morphological abnormalities in erythroid series are erythroid hypoplasia, multinuclearity, dyskaryorrhexis, cytoplasmic vacuolation and/or ring sideroblast. Morphological abnormalities in myeloid series are hypogranularity, increase eosinophils and/or basophils and/or increased blasts. Morphological abnormalities in megakaryocytes are micromegakaryocytes, large mono- or binuclear megakaryocytes and/or megakaryocytes with widely dispersed nuclei. In our study, five patients refused BMA study while one had inconclusive result and refused for repeat BMA study. The other 2 BMAs showed trilineage dysplasia consistent with MDS findings. The centre lacked cytogenetic study at that time.Management options range from observation, supportive care, variety of treatments options (cytotoxics, transplantation, growth factor, immunosuppresion), to get relief of symptoms for those patients whose general health is poor and an improvement in their haematological status would confer least improvement in quality of life. Identification of risk factors for disease progression and use of the IPSS (International Prognostic Scoring System) to predict outcome may help guide the clinicians in deciding patient management {7}.

Treatment of anemia in MDS with EPO plus G-CSF may have a positive impact on outcome in patients with no or low transfusion need, while minimum risk of leukemic transformation {6}.Patients requiring fewer than 2 units of RBC per month have a higher probability of response to EPO plus G-CSF according to the predictive model {8}.New drugs such as 5-azacytidine (azacytidine [Vidaza]), 5-aza-2-deoxycytidine (decitabine [Dacogen]), and lenalidomide (Revlimid) are now approved by the US Food and Drug Administration for myelodysplastic syndrome { 9,10}.

In this study, all patients received red cell transfusions with half of them receiving platelet transfusion. Two patients were given antibiotic therapy and one patient was given EPO treatment. The two confirmed cases in this study were referred to tertiary center for further management. Three patients died, most likely due to complications of severe MDS and one of them was diagnosed with severe community acquired pneumonia (CAP). The remaining 4 patients are still under either HKB or Hospital Universiti Kebangsaan Malaysia (HUKM) follow-up and one patient defaulted follow-up. In conclusion, diagnosis of MDS is considered with pancytopenia and bone marrow examination with cytogenetic study must be performed. Detailed history and clinical examination help rule out other possible causes of cytopenia such as drugs, toxins, radiation exposure, etc. An improved outcome in most cases of MDS is seen with proper treatment.

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Table I. Clinical features of the MDS cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	74	75	68	74	70	68	71	61
Sex	Male	Female	Male	Female	Female	Female	Female	Male
Race	Malay	Malay	Malay	Malay	Malay	Malay	Malay	Malay
Presenting complaint:								
Lethargic	-	+	-	+	+	+	-	+
SOB	-	-	+	-	-	-	+	-
Bleeding tendencies	-	-	-	-	-	-	-	-
Others- Chronic constipation	+	-	-	-	-	-	-	-
Physical examination:								
Pale	+	+	+	+	+	+	+	+
Petechia	-	-	-	-	+	-	-	-
Spenomegaly	-	-	-	-	-	-	-	-
Others- Hepatomegaly	-	-	-	+	-	+	-	-
Heart murmur	-	-	-	-	-	+	-	-

Table II. Laboratory findings of the MDS cases

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**
Laboratory result:								
A) PBF								
Hb (g/dl)	10.4	8.0	3.0	3.2	6.3	5.2	5.9	9.2
Neutrophil (x 10^9/L)	3.0	2.0	1.9	1.8	1.0	3.1	1.5	1.4
Platelet (x 10^3/L)	105.0	12.0	52.0	4.0	18.0	42.0	156.0	136.0
Monocyte (%)	1	3	1	1	5	1	0	1
Reticulocyte count (%)	1.5	1.4	1.1	1.3	1.3	1.5	2.1	1.4
Blast cell	-	+	-	-	-	+	-	-
Bone marrow study	Done	refused	refused	refused	BM study inconclusive	refused	Done	refused
Increase cellularity	+						+	
Dyserythropoeisis	+						+	
Granulocyte precursor	+						+	
Abnormal megakaryocyte	-						+	
Ring sideroblasts	-						-	

Table III. Management and follow ups of the MDS cases

Management	**Pateint 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	patien t 8
Red cell transfusion	+	+	+	+	+	+	+	+
Antibiotic	-	-	+	+	-	-	-	-
EPO	+	-	-	-	-	-	-	-
Platelet transfusion	-	+	-	+	-	+	+	-
Progression	regular follow up	regular follow up	Passed away	regular follow up	Passed away	regular follow up	Default follow up	Passed away

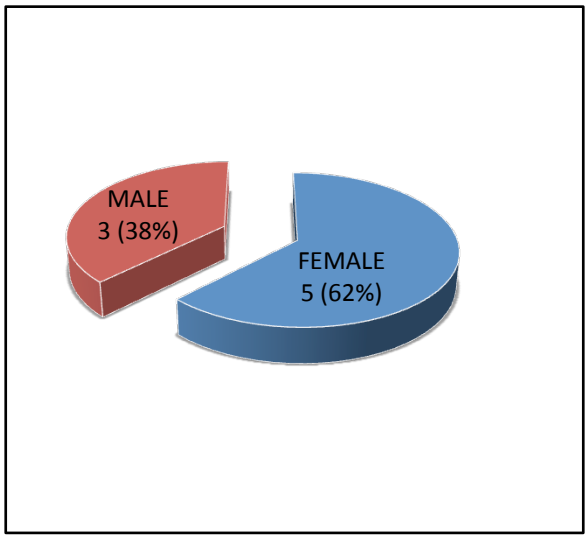


Fig 1. Gender distribution of MDS cases

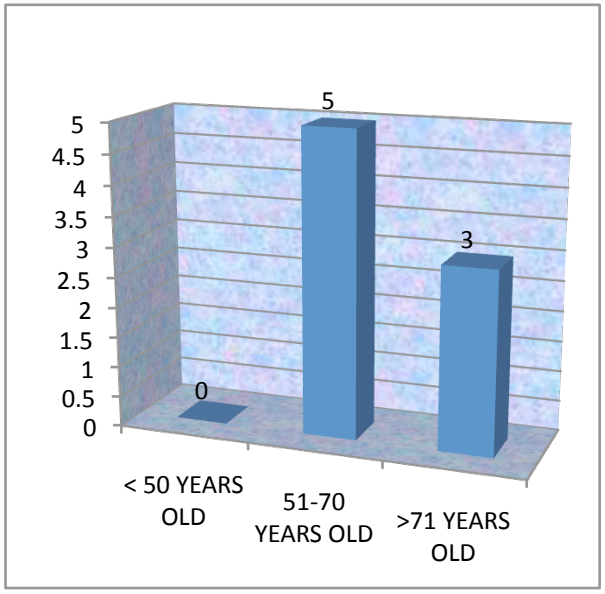


Fig 2. Age distribution for the MDS cases

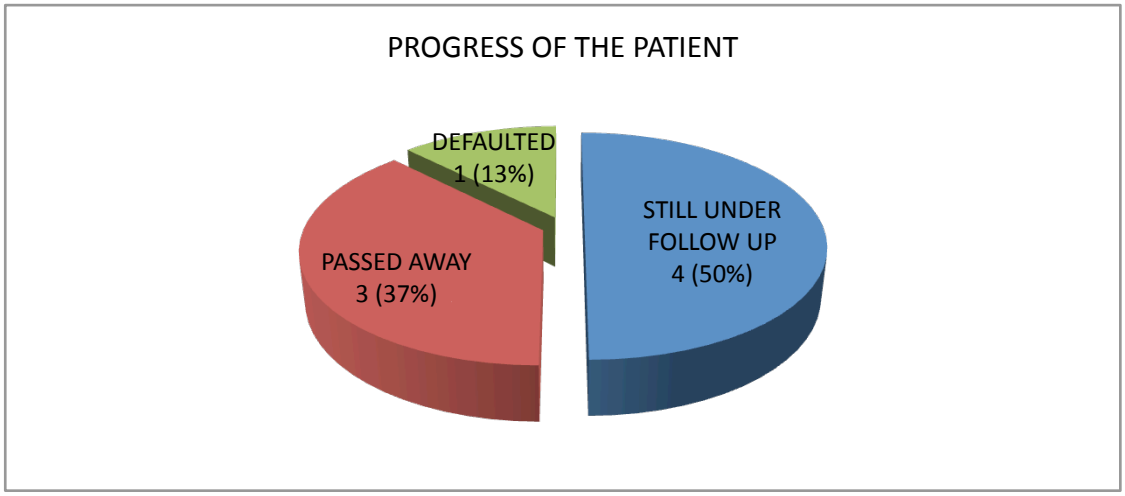
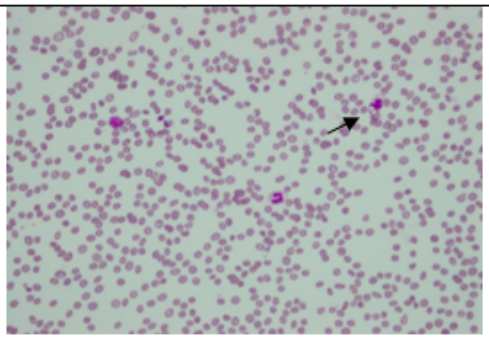
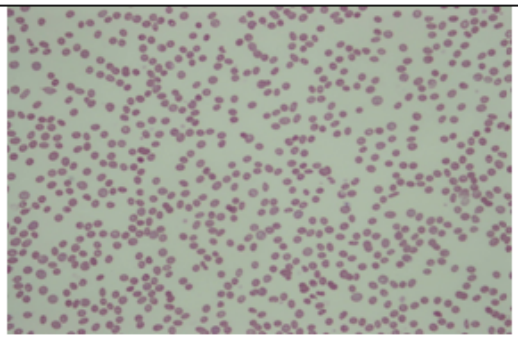


Fig 3. Outcomes of the MDS cases

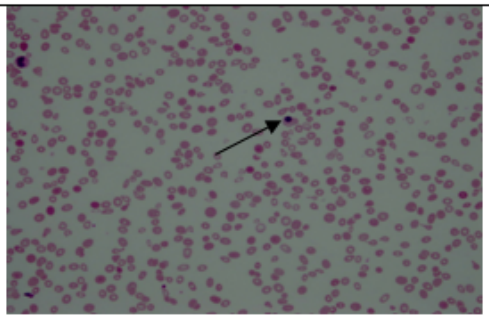
PERIPHERAL BLOOD FILM FINDINGS SEEN IN MDS CASES



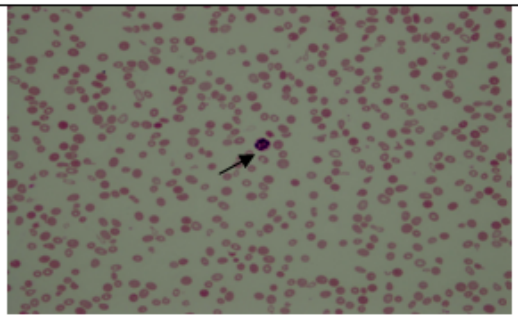
Pic.1: Vacuolated neutrophil



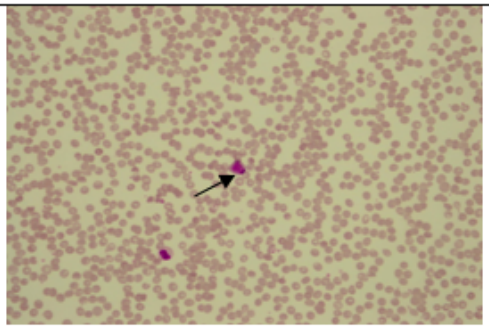
Pic. 2: Dimorphic picture of RBCs



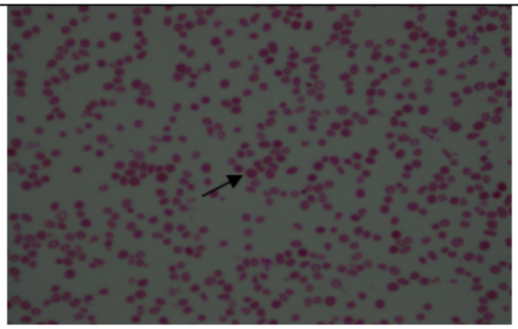
Pic. 3: Nucleated RBC



Pic. 4: Hypersegmented Neutrophil



Pic. 5: PBF showing leucopenia with left shift (arrow showing presence of hypogranular myelocyte)



Pic. 6: PBF showing dimorphic picture with presence of macrocytic cells