MYELODYSPLASTIC SYNDROME: A REVIEW FROM UNIVERSITY HOSPITAL, KUALA LUMPUR

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ABSTRACT

Twenty patients with Myelodysplastic Syndrome (MDS) were diagnosed in University Hospital, Kuala Lumpur over a 5 year period. They were subclassified using the French American British (FAB) criteria. 90% of the patients were above 40 years old and the sex ratio was about equal. The predominant presenting symptom was anaemia and there was paucity of physical signs at presentation. Patients with 'aggressive' subtypes of MDS i.e. refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB – +) and chronic myelomonocytic leukaemia (CMML) had more frequent thrombocytopenia and neutropenia and their marrow pictures frequently had dysmegakaryopoiesis and dysgranulopoiesis as compared to more the "benign" subtypes i.e. refractory anaemia (RA) and refractory leukaemic anaemia with ringed sideroblasts (RARS). Four patients had leukaemic transformation and all of them came from the 'aggressive' subtypes. The current views on treatment of MDS are discussed.

Keywords: Myelodysplastic Syndrome, Leukaemic transformation.

SINGAPORE MED J 1990; Vol 31: 153 - 158

INTRODUCTION

Cases of preleukaemia syndromes preceding onset of acute leukaemia had been recognised since 1900. (1) The term 'Preleukaemia' was first used by Block et al in 1953. (2) Rheingold and his colleagues (3) coined the term 'smouldering leukaemia' to describe patients with similar symptoms and signs of partial bone marrow failure and significant increase in marrow blast cells though not to the level found in acute leukaemia. Other nomenclature were used by different authors such as chronic refractory anaemia with sideroblasts (4), dysmyelopoietic syndrome (5) and haemopoietic dysplasia (6), to describe essentially similar syndromes. In 1982, the French American British (FAB) group (7) proposed that all these conditions be grouped together and described as myelodysplastic syndromes (MDS). Five subtypes of MDS were described and the main distinguishing feature being the percentage of blasts in the bone marrow (Table I).

Table I
French American British Classification of Myelodysplastic Syndrome

	% of blasts in bone marrow %	Ringed sideroblasts >15% of nucleated bone marrow cells	Monocytes >1 x 10^9/L
RA	<5	–	–
RARS	<5	+	–
CMML	<20	–/+	+
RAEB	5-50	–/+	–
RAEB-+	21-30	–/+	–/+

Refractory anaemia (RA)
Refractory anaemia with ringed sideroblasts (RARS)
Chronic myelomonocytic leukaemia (CMML)
Refractory anaemia with excess blasts (RAEB)
Refractory anaemia with excess blasts in transformation (RAEB -+)

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MATERIALS AND METHODS

Between June 1981 to June 1986, 20 patients were diagnosed to have MDS in the University Hospital. The case notes and haematological slides were reviewed by the first two authors. The patients were classified using the FAB group criteria. Cases having dysmyelopoiesis secondary to vitamin B_{12} or folic acid deficiency were excluded.

RESULTS

Patients' Characteristics

90% of the patients were more than 40 years old. The age range was 6 years to 77 years. The male to female ratio was about equal (9:11) (Fig 1).

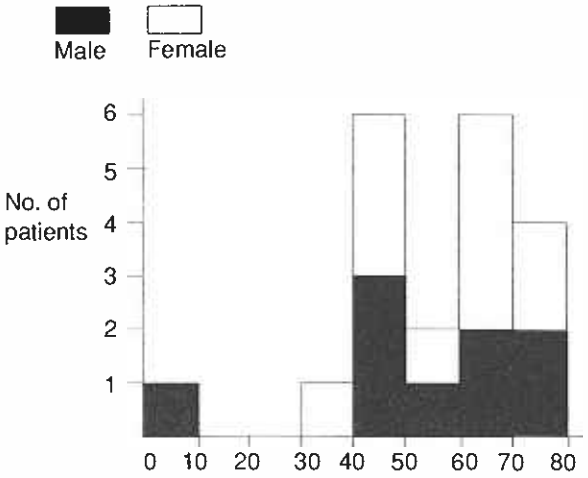

Fig 1:
Age and Sex Distribution of Patients

Clinical Features

Symptoms related to anaemia were the predominant presenting problem in 80% of patients (Table II). Pallor was present in all the patients. There was a paucity of physical signs. Hepatosplenomegaly was noted in two patients and none had significant lymphadenopathy (Table III).

Classification of Patients

19 patients could be classified into one of the groups of FAB group classification (Table IV) while one patient who had MDS with dysgranulopoietic neutrophilia was listed as unclassified. With one exception, all the other cases were considered to have primary MDS. The patient

Table II
Presenting Complaints

Symptoms	No. of cases
Anaemia	16
Bleeding	2
Infection	1
Asymptomatic	1
Total	20

Table III
Clinical Signs

	No. of cases
Pallor	20
Lymphadenopathy	–
Hepatosplenomegaly	2

with secondary MDS had prior chemotherapy with alkylating agents (cyclophosphamide and chlorambucil) for treatment of carcinoma of ovary 7 years before onset of MDS.

Haematological Profile

Peripheral cytopenia(s) was evident in all patients. Pancytopenia was present in 7 patients. 90% of patients had Hb < 8g% at time of presentation. Thrombocytopenia < 150 x 10^9/dL was present in 11 (55%) patients while leucopenia < 4 x 10^9/L was seen in 8 (40%) patients. Patients with 'aggressive' subtypes (i.e. RAEB, RAEB-+) tended to have cytopenia in more than one cell line and 3 of them had blasts in the peripheral blood films (Table V). Prominent peripheral blood film morphological abnormalities were present in all cases (Table VI). The common findings were macrocytosis, dimorphic picture, poikilocytosis, occasional nucleated red cells and hypogranular neutrophils, Pelgar-Huet like abnormality as well as occasional giant platelets.

Bone Marrow Examination

Bone marrow aspirations were done for all patients while only 8 of them had trephine biopsies performed. Hypercellular marrow was noted in 13 patients (65%), normocellular marrow in 5 patients and in one patient the cellularity could not be assessed due to lack of marrow fragments. Only one patient (patient with secondary MDS) had hypocellular marrow. Myelodysplasia, (Fig. 2,3) the cornerstone for clinching the diagnosis was usually confined to the erythroid lineage in RA and RARS while in RAEB and RAEB-+ both dysgranulopoiesis and dysmegakaryopoiesis were present concurrently (Table VII).

Trephine biopsies also showed presence of dysgranulopoiesis and dysmegakaryopoiesis in patients

Table IV
Subtypes of MDS

Subtypes	No. of patients
RA	7
RARS	3
RAEB	4
RAEB - +	4
CMML	1
Unclassified	1
Total	20

Table V
Blood Counts at Presentation

	RA	RARS	RAEB	RAEB -+	CMML	Unclassified	Total
Number of patients	7	3	4	4	1	1	20
Hb (g%) < 5	2	1	1	1	–	–	5
5 – <8	4	2	3	3	1	–	13
8 – 11	1	–	–	–	–	1	2
WBC < $4x10^9$/L	2	2	2	2	–	–	8
Platelet < $150x10^9$/L	4	1	3	3	–	1	11
Pancytopenia	2	1	2	2	–	–	7
Circulatory blasts	–	–	1	2	–	–	3

Table VI
Peripheral Blood Morphology

Prominent Morphological Abnormality	No. of Patients
Macrocytosis	5
Dimorphic picture	4
Poikilocytosis	6
Hypogranular neutrophils	4
Giant platelets	3

with RAEB-+ more frequently than patients with RA and RARS (Fig. 4). The cellularity was increased in 6 out of the 9 patients with trephine biopsies done. Increased reticulin fibres were detected in 5 patients (Table VIII).

Fig 2
Bone marrow aspirate showing dysplastic binucleated megakaryocytes. MGG x 800

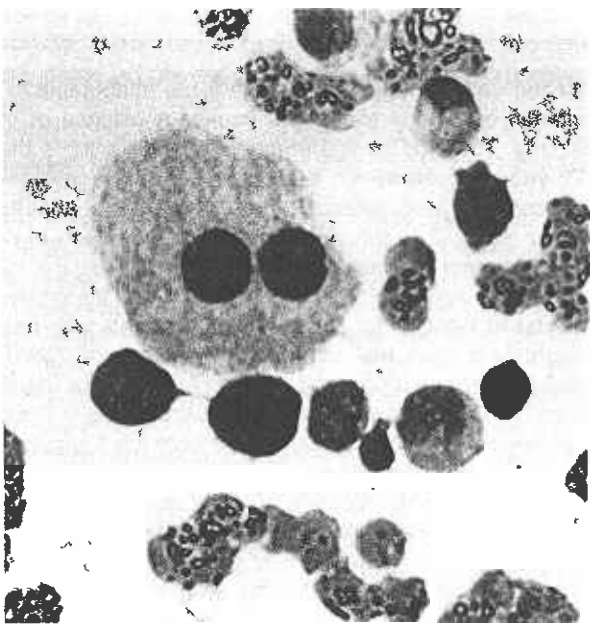

Fig 3
Bone marrow aspirate showing presence of myeloblasts with hypogranular myelocyte in a patient with RAEB. MGG x 800

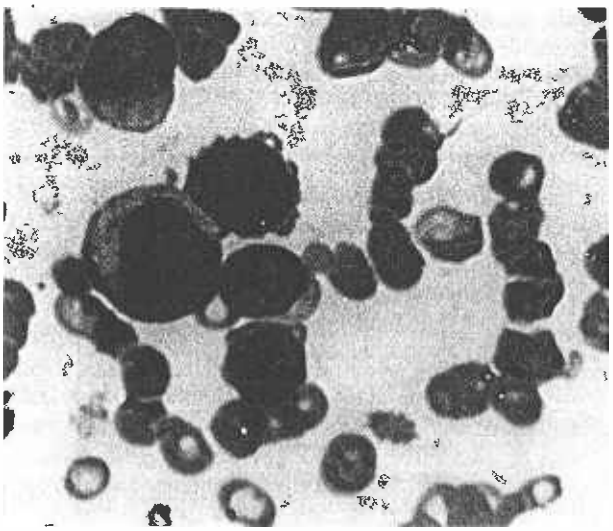

Fig 4
Trephine biopsy showing hypercellur marrow with marked dysmegakaryopoiesis. H&E x 400

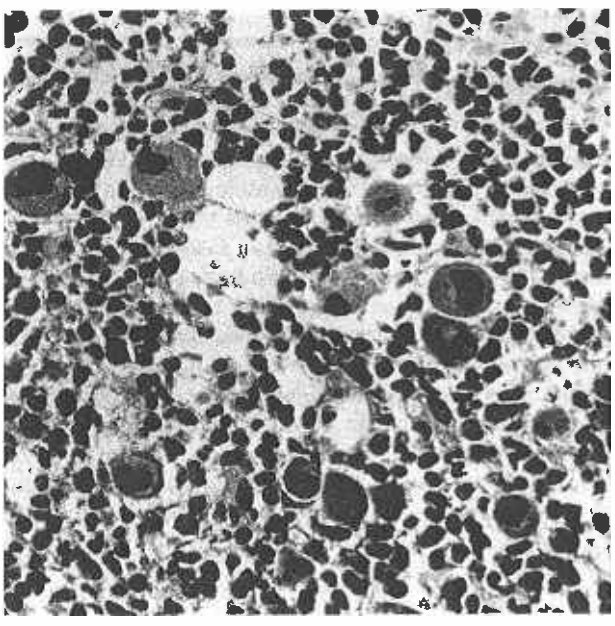

Table VII
Bone Marrow Aspirate Findings

	RA	RARS	RAEB	RAEB-+	Total
Number of patients	7	3	4	4	18
Dyserythropoiesis	7	3	4	4	18
Dysgranulopoiesis	3	–	3	4	10
Dysmegakaryopoiesis	3	–	4	3	10

- Dyserythropoiesis: The abnormalities include presence of ringed sideroblasts, multinuclearity, nuclear fragments, abnormal nuclear shape and normal cytoplasmic features.
- Dysgranulopoiesis: The abnormalities include a granular or hypogranular neutrophils, nuclear abnormalities either that of hyposegmentation (Pelger-Huet like abnormality) or hypersegmentation with bizarre shapes.
- Dysmegakaryopoiesis: The abnormalities include micromegakaryocytes, large mononuclear megakaryocytes and megakaryocytes with multiple small separated nuclei.

Table VIII
Trephine Biopsies Findings

	RA	RARS	RAEB	RAEB -+	Total
No of patients	3	1	3	1	8
Red cell series:					
quantitatively disturbed	0	0	3	1	4
dyserythropoiesis	3	1	3	1	8
normal	0	0	0	0	0
White cell series:					
quantitatively disturbed	1	0	1	1	3
dysgranulopoiesis	1	0	3	1	5
normal	1	1	0	0	2
Megakaryocytic series:					
quantitatively disturbed	0	0	2	1	3
dysmegakaryopoiesis	1	1	0	0	2
normal	1	1	0	0	2
Increased reticulin	1	0	3	1	5
Cellularity:					
increased	1	1	3	1	6
normal	2	0	0	0	2
decreased	0	0	0	0	0

Outcome

The period of follow up ranged from those who defaulted even the first follow up (2 patients) to $2^1/_2$ years. The high default rate could be partly attributed to the patients' realisation that no specific curative therapy was given. Despite the gross inadequacies in follow up, 4 patients were noted to undergo leukaemic transformation (Fig.5). Acute myeloid leukaemia was diagnosed in these patients (Table IX). The time lapse between diagnosis of MDS and leukaemia transformation ranged from one month to 8 months. 6 deaths were recorded; 3 amongst the transformed cases while 2 died as a result of cytopenia without evidence of transformation and 1 patient died of an unrelated cause.

DISCUSSION

MDS is a clonal stem cell disorder characterised by persistent peripheral blood cytopenia(s) usually in the presence of a hypercellular marrow with features of ineffective haemopoiesis which are not attributable to a vitamin deficiency state. It is usually a disease of the elderly. The median age in most series was more than 70 years (8). However, it can occur in any age group. Almost all patients presented with symptoms of anaemia in our study. The paucity of physical signs seen in our patients were also reported in other studies (9).

The haematological profile of our MDS patients were similar to those of other series (10). Patients with more aggressive subtypes (i.e. RAEB, RAEB-+ and CMML) had frequent neutropenia and thrombocytopenia usually with prominent dysgranulopoiesis and dysmegakaryopoiesis. Four patients from the 'aggressive' subtype were noted to undergo leukaemic transformation. Hence, the FAB classification was a very useful prognostic marker as found in other studies(11).

The diagnosis of MDS is difficult in the early stage of MDS and this is aggravated by *no* generally accepted diagnostic criteria. It is important to distinguish MDS from benign haematological disorders with maturation

Fig 5
Bone marrow aspirate showing mainly myeloblasts in MDS patient who underwent leukaemic transformation. MGG x 800

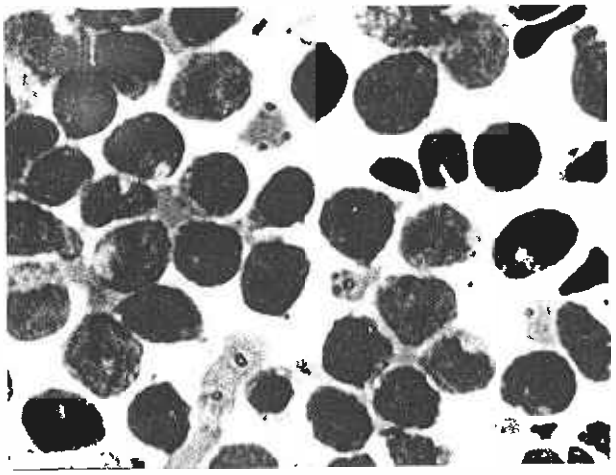

Table IX
MDS Patients That Underwent Leukaemic Transformation

No. of patients		No. transformed
• RAEB	4	1
• RAEB -+	5	3
• RA	7	–
• RARS	3	–
Total	19	4

abnormality of bone marrow e.g. anaemia caused by chronic infection, systemic diseases, liver diseases and alcohol induced bone marrow changes. In cases of doubt, cytogenetic studies and close follow-up would usually provide the answer. Four patients in our series required repeated bone marrow examination before the diagnosis was made. Hypoplastic anaemia with dyserythropoiesis may pose difficulty in diagnosis (12). The reduced cellularity and reduced or absent megakaryocytes in hypoplastic anaemia were useful differentiating points from MDS.

The trephine biopsy is valuable in the diagnosis and evaluation of prognosis of patients with MDS. It provides accurate assessment of marrow cellularity. The detection of abnormal localization of immatured precursors (ALIP) confers a poor prognosis (13). This was not detected in any of our patients. Dysmegakaryopoiesis is more conspicuous and increase in reticulin fibres can be demonstrated in trepine sections. Moreover, other stroma reactions such a oedema, ectatic sinus, inflammatory reactions, etc. have been described (14) though the significance is not known.

TREATMENT

The management relies on providing haematological support. The specific treatment of the disorder is controversial but may include low dose cytosine arabinoside (Ara-C) (15) to induce differentiation in the abnormal haemopoietic precursors or intensive chemotherapy to eradicate the underlying abnormal clone. Before planning therapy, it is important to identify patients with good prognosis since even low dose chemotherapy may lead to unacceptable morbidity and mortality. For 'aggressive' subtypes i.e. RAEB-+, intensive chemotherapy followed by bone marrow transplant (BMT) is being evaluated as a mode of treatment for young patients with suitable matched donors.

In secondary MDS the morphological dysplastic features seen in cells of blood and bone marrow are indistinguishable from those found in primary MDS. However, secondary MDS patients tend to be younger with hypocellular marrow and karyotypic abnormality present almost every case. Their prognosis is poorer due to development of acute leukaemia (16).

CONCLUSION

The potentially serious nature of MDS warrants a reasonably high index of suspicion and a precise diagnosis in each patient. MDS should be looked for in patients with pancytopenia or macrocytic anaemia. Patients with RAEB, RAEB-+ and CMML should be followed up closely for evolution of acute leukaemia.

REFERENCES

1. Hast R: The preleukemic syndrome. MD thesis. University of Stockholm, 1979.
2. Block M, Jacobson LO, Bethard WF: Preleukemic acute human leukemia. JAMA 1953; 152: 1018-23.
3. Rheingold JJ, Kaufman R, Adelson E, Lear A: Smouldering acute leukaemia. New Engl J Med 1963; 268: 812-6.
4. Bjorkman SD: Chronic refractory anemia with sideroblastic bone marrow. Blood 1956; 1: 250-9.
5. Streuli RA, Testa JR, Vardiman JW, et al: Dysmyelopoietic syndrome: sequential, clinical and cytogenetic studies. Blood 1980; 55: 636-44.
6. Linman JW, Baghy GC: The preleukemic syndrome (Hemopoietic Dysplasia). Cancer 1978; 42: 852-64.
7. Bennet JM, Catovsky D, Daniel MT, et al: Proposals for classification of the myelodysplastic syndrome. Br J Haematol 1982; 51: 89-99.
8. Galton DAG: The myelodysplastic syndromes. Scan J Haematol 1986; 36 (Suppl 45): 11-20.
9. Foucar K, Langdon RM, Armitage JO, Daniel BO, Thomas JC: Myelodysplastic syndrome. A clinical and pathologic analysis of 109 cases. Cancer 1985; 56: 553-61.
10. Weber RFA, Geraedts JPM, Kerkhofs H, Leeksma CHW: The preleukemic syndrome. Acta Med Scan 1980; 207: 391-5.
11. Coiffier B, Adeline P, Viala JJ et al: Dysmyelopoietic syndrome: A search for prognostic factors in 193 patients. Cancer 1983; 52: 83-90.

12. Frisch B, Lewwis SM: The bone marrow in aplastic anemia: Diagnostic and prognostic features. J Clin Path 1974; 27: 231-41.
13. Tricot G, Vlietink R, Boogaerts MA et al: Prognostic factors in the MDS: Importance of initial data on peripheral blood counts, bone marrow cytology, trephine biopsy and chromosomal analysis. Br J Haematol 1985; 60: 19-32.
14. Frisch B, Bartl R: Bone marrow history in MDS. Scan J Haematol 1986; 36 (Suppl 45): 21-37.
15. Buccarani M, Zaccania A, Bandini G et al: Low dose arabinoside cytosine for treatment of MDS and subacute myeloid leukemia. Cancer Res 1983; 8: 539-45.
16. Tricot G, Boogaerts MA, Vorwillghen RL: Treatment of patients with MDS: A review. Scan J Haematol 1986; 36 (Suppl 45): 121-7.