Refractory myelodysplastic anaemias with hypocellular bone marrow

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SUMMARY Thirty three patients with refractory myelodysplastic anaemias (RMDA) with marrow hypocellularity were reviewed to see whether they differed from those with normocellular or hypercellular marrows.

The median age was 65 years with a male:female ratio of 26:7. There were 11 cases of refractory anaemia (RA), four of refractory anaemia with ringed sideroblasts (RARS), and 18 of refractory anaemia with excess of blasts (RAEB). All presented with peripheral cytopenias, mostly pancytopenia or bicytopenia, dysplasia in one or more cell lineages, and a marrow biopsy specimen with less than normal numbers of nucleated cells for the age. Twenty four patients died, including 14 of the 16 who developed acute non-lymphocytic leukaemia (ANLL).

The results suggest that patients with hypocellular RMDA have a similar prognosis to those with normocellular or hypercellular marrows at presentation.

Since the term myelodysplastic syndromes (MDS) was coined, several studies have reported on the clinicopathological, biological, and prognostic aspects,¹⁻⁶ but whether patients with marrow hypocellularity should be excluded has been a matter for controversy. Most authors have restricted the term MDS to those with normocellular to hypercellular marrow^{2,7-9}, though others,¹⁰⁻¹⁴ on the basis of bone marrow biopsy findings, have included patients with varying degrees of marrow hypocellularity as well. This second option has not been fully accepted by most haematologists.

This paper describes the clinical and pathological features of patients with hypocellular refractory myelodysplastic anaemias (RMDA) and compares their natural history with that of normocellular to hypercellular cases. The term RMDA is retained here to encompass the three major subtypes of MDS; refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), and refractory anaemia with excess of blasts (RAEB).

Material and methods

Data from 33 cases (26 men, seven women) of RMDA with marrow hypocellularity were reviewed. The median age was 65 years, range 26-92 years. They represented 7.7% of a total of 428 cases of RMDA registered by the Japanese Cooperative Study Group

up to April 1987. Follow up ranged from five to 152 months. All fulfilled the diagnostic criteria set out by the group.^{15,16} RAEB and evolution to ANLL were diagnosed according to the FAB classification.² RARS was defined as ringed sideroblasts comprising more than 20% of marrow erythroblasts.¹⁵ Cases not meeting the criteria for RAEB or RARS, yet showing cellular dysplasias or normocellular to hypocellular marrow, or a combination, were defined as RA.¹⁵ Excluded were those with myeloproliferative disorders, aplastic anaemias, deficiencies, or a history of exposure to myelotoxic agents.^{15,16}

When the marrow aspirates showed a normal to increased cellularity in smears a cellular marrow was diagnosed, but in cases with a decreased cellularity in smears, the marrow cellularity was evaluated in sections of iliac crest biopsy specimens obtained with the Jamshidi needle.¹⁷ Hypocellularity was defined in biopsy sections relative to the normal range of iliac marrow cellularity in a given age group.¹⁸ The bone marrow biopsy specimen was therefore considered to be hypocellular when less than 30% of the marrow consisted of haemopoietic cells in patients below 60 years and less than 20% in patients older than 60 years. Although this is arbitrary and there is a considerable variation in the distribution of fat and haemopoietic cells,¹⁸ this definition of marrow hypocellularity is comparable with that of most other investigators.¹⁹⁻²¹

Dysplasias of blood and marrow cells were recorded

Table 1 Clinical and haematological data of patients with RA and RARS showing hypocellular marrow

Case No	Age/Sex	Peripheral blood						Bone marrow		
		Haemoglobin (g/dl)	Neutrophils ($10^9/l$)	Platelets ($10^9/l$)	Reticulocytes (%)	Lymphocytes (%)	Blasts (%)	Lymphocytes (%)	Blasts (%)	Ringed sideroblasts (%)
RA:										
1079	51/M	6.2	0.81	46	0.5	68.0	0	75.4	1.8	0*
2006	75/M	9.1	3.34	197	3.0	31.5	0	15.2	3.0	0
2031	46/M	9.9	0.87	200	1.7	54.0	0	34.5	0.3	12
2045	62/M	6.5	1.05	80	2.8	63.0	0	6.0	0.5	0
2081	70/F	9.2	2.99	241	0.9	31.0	0	4.5	0.5	1
2091	46/M	3.4	0.77	90		47.0	0	47.6	3.4	0
2095	56/M	10.5	0.43	190		65.0	0	32.0	1.4	0
2121	71/M	8.1	2.80	112	0.5	59.5	0	38.0	2.4	0
2506	25/M	7.1	1.30	110	1.7	25.0	0	29.2	0.8	0
2715	82/F	6.3	0.78	14	0.2	65.0	0	27.8	0	0.2
2724	57/M	8.5	1.02	83	0.2	55.0	0	5.2	4.6	0.2
RARS:										
8	69/F	7.5	1.84	337	5.1	37.0	0	15.6	0.8	72
42	29/M	8.6	0.46	172	2.1	60.0	0	2.8	0	23
43	76/M	4.7	1.60	36	1.8	48.0	0	10.6	3.4	58
705	92/F	7.1	1.71	155	0.3	40.0	0	23.2	2.4	45

PID: Plasma iron disappearance, RCU: Red cell iron utilisation, *% of total marrow erythroblasts, †follow up ended with patient's death.

as none (—), moderate (+), and pronounced (++), based on the prevalence and degree of the abnormality within each cell lineage.¹⁵ Briefly, 500 cell myelograms were performed. Dyserythropoiesis and dysgranulopoiesis was defined as (+) or (++) if one or more than two of the following morphological changes were present in each cell lineage. There were megaloblastoid changes, other nuclear anomalies such as multinuclearity, and ringed sideroblasts in the erythroid series; and nuclear and granular abnormalities in the granulocytic series. At least 20 megakaryocytes were examined separately for the presence of micromegakaryocytes and megakaryocytes with small round nuclei, in addition to giant platelets in the blood film.

Other variables analysed included serial blood and marrow differential counts, percentage of ringed sideroblasts, and ferrokinetic, cytogenetic, and marrow cell culture data. Statistical analysis of the prognostic variables was performed as described elsewhere.¹⁵

Results

HYPOCELLULAR RA AND RARS

Table 1 details the clinical and haematological data of 15 patients with hypocellular RA and RARS. All were anaemic at the time of presentation. Eight had a platelet count of less than $150 \times 10^9/l$ and 12 a

Table 2 Clinical and haematological data of patients with RAEB showing hypocellular marrow

Case No	Age/Sex	Blood						Marrow	
		Haemoglobin (g/dl)	Neutrophils ($10^9/l$)	Platelets ($10^9/l$)	Reticulocytes (%)	Lymphocytes (%)	Blasts (%)	Lymphocytes (%)	Blasts (%)
1005	71/M	9.2	0.33	28	2.5	60.0	2.0	20.8	14.8
1013	71/F	8.8	0.10	66	1.0	82.0	0	17.7	6.0
1043	83/M	5.2	0.79	267	2.0	54.0	2.0	16.8	16.8
1044	73/F	7.2	0.82	40	1.2	40.0	3.0	16.2	8.0
1048	76/M	6.4	0.39	121	0.5	30.5	0	42.0	12.8
1050	54/M	12.5	0.05	64	0.1	94.0	0	64.0	12.0
1060	61/M	8.8	0.50	36	1.3	80.0	0	22.0	18.0
1063	73/F	11.1	0.57	100	0.9	70.0	0	34.0	12.5
1076	60/M	10.2	0.67	76	1.0	36.0	0	4.4	13.0
1084	40/M	5.9	1.25	147	0.5	41.0	0	52.0	6.0
1101	65/M	11.1	1.46	154	2.8	53.0	0	31.2	14.0
1115	57/M	11.2	0.66	68		61.0	0	19.2	11.0
1502	61/M	6.4	0.13	19	2.0	87.0	0	20.0	19.1
1508	52/M	7.3	0.84	30	0.1	63.0	0	32.7	11.4
1705	77/M	11.7	0.75	69	2.0	70.0	0	28.0	16.0
1735	62/M	5.4	0.30	77	0.4	67.0	2.0	36.3	14.3
1741	66/M	8.1	0.27	225	2.2	67.0	2.0	8.1	9.9
1750	65/M	6.6	0.41	128	0.1	68.0	0	29.2	9.6

PID: Plasma iron disappearance, RCU: Red cell iron utilisation, †followup ended with patient's death.

Ferrokinetics		Dysplasia			Chromosome anomaly	Outcome		
PID (minutes)	RCU (%)	Dyserythropoiesis	Dysgranulopoiesis	Dysmegakaryopoiesis		ANLL	Survival (months)	Cause of death
116	ND	—	+	+	—	+	30.0†	Infection
125	69	++	++	+	—	—	20.7	Bleeding
280	57	+	—	—	ND	—	40.1†	
165	52	—	—	+	ND	—	20.0	
	77	++	—	—	ND	—	15.8	
	ND	++	++	+	—	+	8.6†	Infection
105	ND	+	++	+	—	—	24.0†	Unknown
126	5	—	+	++	—	+	11.0†	Unrelated death
	83	—	—	+	ND	—	113.0	
121	ND	++	—	—	ND	—	44.0	Unrelated death
	9	++	++	+	+	—	12.0	
36.5	18	+	—	—	—	—	14.0†	
252	40	+	+	++	+	—	61.0	
153	40	+	+	++	+	—	38.0†	Infection
54	63	++	—	—	—	—	24.0†	Unrelated death

neutrophil count of less than $2 \times 10^9/l$. The median lymphocyte count in the blood was 54.0% with a range of 25–68% while that in the marrow was 23.2% with a range of 2.8–75.4%. Eight showed dysplasia in more than two cell lineages. Dysplasia was confined to single cell lineage in seven, notably erythroid in five, and megakaryocytic in two patients. Ferrokinetic data were available in 11 patients. Only two patients showed an aplastic pattern—that is, prolonged plasma iron disappearance and decreased red cell utilisation of radioiron. Some patients also showed a near normal growth of haemopoietic colonies in marrow cell cultures despite marrow hypocellularity (data not shown). Four of the five in whom dysplasia was confined to erythroid lineage showed a normal to shortened plasma iron disappearance, a decreased red

cell utilisation, and a nearly normal platelet count. Eight patients died, including three who developed ANLL.

HYPOCELLULAR RAEB

All 18 patients presented with varying degrees of pancytopenia except for two with normal platelet counts (table 2). All had a relative lymphocytosis in the blood. The median marrow lymphocyte was 25% with a range of 4.4–64.0%. The marrow blast cell was 6–19.1%. Tricellular lineage dysplasia was found in six patients. Dysplasia in two cell lineages was found in seven patients, while single cell lineage dysplasia was found in five—that is, three myeloid and two erythroid. Sixteen patients died, including 11 of the 13 who developed ANLL. The main causes of death were

Ferrokinetics		Dysplasia			Chromosome anomaly	Outcome		
PID (minutes)	RCU (%)	Dyserythropoiesis	Dysgranulopoiesis	Dysmegakaryopoiesis		ANLL	Survival (months)	Cause of death
180	70	—	+	—	—	+	14.0†	Infection
67	23	—	+	—	—	—	7.4†	Infection
	ND	—	+	+	+	—	5.0†	Renal failure
	ND	+	+	+	—	+	24.0†	Infection
	ND	+	++	—	ND	—	14.4†	Infection
200	5.2	+	+	++	—	+	6.7†	Infection
	ND	+	+	—	ND	+	7.2†	Infection
155	95	++	+	++	ND	+	67.0	Bleeding
175	46.2	+	+	+	+	+	4.7†	
	ND	++	+	+	—	+	5.4†	
	ND	—	+	++	—	+	3.0†	
	ND	++	+	++	ND	+	22.7	Infection
	ND	++	+	—	—	—	20.0†	
33	15	++	+	—	+	+	1.4†	
	ND	+	—	—	ND	+	18.0†	
	ND	++	+	—	ND	—	18.7†	Infection
	ND	+	—	—	—	+	7.7†	Infection
	ND	—	+	—	ND	+	13.3†	Infection

infections in 13, and bleedings in three. The patients with hypocellular RAEB tended to have a higher incidence of evolution to ANLL than those with normocellular to hypercellular marrow (data not shown). There was no significant difference in the leukaemia free survival between the two groups ($\chi^2 = 3.123$, Mantel-Cox test, $0.1 > p > 0.05$). Similarly, these two groups did not differ significantly in survivals ($\chi^2 = 2.57$, $p > 0.1$) or in the rate of non-leukaemic death ($\chi^2 = 0.681$, NS).

Discussion

This study shows the presence of marrow hypocellularity confirmed by biopsy in a small proportion (7.7%) of patients with RMDA. Hypocellular RMDA was distinct from aplastic anaemia in cellular dysplasia, cytogenetic and ferrokinetic findings, and a high rate of evolution to ANLL (tables 1 and 2). Hypocellular RAEB also differed from hypoplastic leukaemia in the percentage of marrow blasts. The percentage of marrow blasts is usually greater than 30% in hypoplastic leukaemia,¹⁹ although some overlapping cases have been reported.^{20,22}

A somewhat higher incidence of hypocellular MDS has been reported where marrow histology has been assessed by trephine biopsy.^{11,13,23} As not all cases showing cellular marrow in aspirates were studied by trephine biopsy, the proportion of observed hypocellular RMDA may be an underestimate of the true percentage of hypocellularity. Estimation of marrow cellularity usually shows a good correlation between smears of aspirates and biopsy specimens but this correlation may be lost in MDS, probably due to pronounced topographic variation. Variability of cellularity^{11,12} and irregular distribution of haemopoietic cells^{13,23,24} seem to be histological characteristics of MDS. Such topographic variability may explain the discrepancy occasionally seen in this study between marrow cellularity and ferrokinetic findings (tables 1 and 2). In addition, ferrokinetic findings are a measure of the erythropoietic activity of the whole body and do not necessarily correspond to the marrow cellularity of a single marrow site, to which many non-erythroid cells may contribute. As aspirations and biopsies are mutually complementary, both procedures, preferably from different sites, are required to evaluate marrow cellularity reliably.

Several factors may account for marrow hypocellularity in RMDA which usually shows cellular marrow. First, hypocellular myelodysplasia may precede hypercellular myelodysplasia.¹⁴ Although in the present series repeat biopsy specimens were not taken in every case, this possibility is unlikely as some remained hypocellular throughout follow up and hypocellularity was found to the same degree in all

three subtypes of RMDA.

Secondly, hypocellular RMDA may represent a distinct clinicopathological entity. Hypocellular marrow with increased blasts has been characterised by an association with exposure to myelotoxic agents, severe marrow failure, and a poor response to chemotherapy.²¹ Marrow hypocellularity and fibrosis have been seen in secondary or mutagen-related MDS/ANLL¹⁻³ though in our study no patients with a known history of myelotoxic exposure were included. A recent report suggested that among MDS patients those with hypocellular marrow developed leukaemia less often, responded to androgens more often, and survived longer than those with cellular marrow.²⁵ We have found no evidence to support this. Our patients showed no significant difference in overall survival, leukaemia free survival, or death from other causes among those with hypocellular or cellular RMDA. In fact, patients with hypocellular RAEB tended to be at even higher risk of developing ANLL than those with cellular RAEB. The exact nature of the hypocellular RMDA or the suggestion that damage to the marrow may manifest itself in several ways²⁶ remains to be investigated further.

Hypocellularity in single marrow aspirates does not preclude the diagnosis of RMDA. Trephine bone marrow biopsy specimens obtained from different sites are needed to make the diagnosis.²⁷ The fact that hypocellular RMDA does exist should be borne in mind when planning the treatment of these enigmatic disorders.

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