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SPECIAL CONTRIBUTION

First Cytogenetic Profile of Omani Patients with *de novo* Myelodysplastic Syndromes

Comparison with data from Asia, Africa, Europe and North and South America

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أول ملف للجينات الخلوية للمرضى العمانيين المصابين بمتلازمة خلل النسج النقوي

مقارنة مع بيانات من اسيا وافريقيا وامريكا الشمالية والجنوبية

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ABSTRACT: Clonal cytogenetic abnormalities have been reported among 30–80% of patients with myelodysplastic syndromes (MDS); however, 20–70% of patients with MDS show a normal karyotype that may nevertheless harbour a cryptic genetic alteration. Earlier reports have suggested that the distribution of specific chromosomal aberrations varies among Western and Asian countries, with geographical and ethnic differences in the frequency of specific chromosomal aberrations. This article compared the cytogenetic data of 36 adult Omani patients with MDS to previously reported data from other populations. Differences were noted between the percentages of clonal aberrations and the median age of Omani subjects at presentation in comparison to individuals of different ethnicities and from various geographical locations. To the best of the authors' knowledge, this is the first report to describe the cytogenetic data of patients with MDS from Oman.

Keywords: Cytogenetic Abnormalities; Chromosomal Aberrations; Myelodysplastic Syndromes; Population Heterogeneity; Ethnic Groups; Oman.

الملخص: توجد تقاريرعن تشوهات للجينات الخلوية بين 30–80% من المرضى الذين يعانون من متلازمات خلل التنسج النقوي ومع ذلك فأن، 20–70% من المرضى الذين يعانون من هذه المتلازمة تظهر لديهم النمط النووي العادي الذي قد يؤوي تغيير وراثي خفي. وقد أشارت تقارير سابقة إلى أن هناك توزيع كروموسومي شاذ محدد يتفاوت بين البلدان الغربية والآسيوية، مع وجود اختلافات جغرافية وعرقية في تواتر الانحرافات الصبغية المحددة. وقد قارنت هذه المقالة بيانات الوراثة الخلوية ل 36 مريضا عمانيا بالغين يعانون من متلازمة خلل النسج النقوي إلى بيانات سبق الإبلاغ عنها من شعوب أخرى. وقد لوحظت فروق بين نسب الانحرافات النسيلية والعمر الوسيط للمواطنين العمانيين عند بداية المرض مقارنة بأفراد من مختلف الأعراق ومن مختلف المناطق الجغرافية. إلى حد علم المؤلفين، هذا هو أول تقرير لوصف البيانات الخلوية الجينية للمرضى الذين يعانون من متلازمة خلل النسج النقوي من عمان.

الكلمات المفتاحية: تشوهات خلوية المنشأ؛ شذوذ الكروموسومات؛ متلازمات خلل التنسج النقوي؛ عدم التجانس السكاني؛ جماعات عرقية؛ عمان.

Myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterised by cytopaenia, dysplasia in one or more of the major myeloid cell lines, ineffective haematopoiesis and an increased risk of developing acute myeloid leukaemia (AML).[1] Cytogenetic and molecular abnormalities are key elements in the diagnosis of MDS. Clonal chromosomal abnormalities in MDS have been observed in 30–80% of patients, depending on the subtype and whether it is *de novo* or mutagen-induced.[2,3] For the other 20–70% of MDS patients with normal karyotypes, there is substantial evidence for the presence of submicroscopic alterations—such as point mutations, microdeletions, microamplifications, epigenetic changes or copy number neutral loss of information—which may form the genetic basis of the disease.[4–6] The percentage of clonal abnormalities in the literature varies between 23–78%.[7–9]

Over time, MDS has been increasingly recognised as a cause of bone marrow failure; however, the precise incidence of *de novo* MDS is unknown.[10] Jacobs *et al.* have suggested that the distribution of specific chromosomal aberrations in MDS varies between Western and Asian countries.[11] Another report also indicated geographical and ethnic differences in the frequency of specific chromosomal aberrations.[12] The incidence of chromosomal abnormalities

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Table 1: Characteristics of Omani patients with myelodysplastic syndromes presenting to the Sultan Qaboos University Hospital, Muscat, Oman (N = 36)

Characteristic	n (%)
Gender	
Male	18 (50.0)
Female	18 (50.0)
Age in years	
Mean/median (range)	63/65 (16–86)
>60	23 (63.9)
<60	13 (36.1)
Peripheral blood count	
Median haemoglobin in g/dL (range)	8.7 (6.2–14.9)
Median ANC in $x10^9$/L (range)	1.3 (0.1–31.5)
Median platelet count in $x10^9$/L (range)	77 (5–591)
Cytopaenia	
None	1 (2.8)
Single lineage	7 (19.4)
Bilineage	15 (41.7)
Trilineage	13 (36.1)
Bone marrow blast in %	
<5	27 (75.0)
5–10	5 (13.9)
>10	4 (11.1)
Therapy	
Supportive only	29 (80.6)
Chemotherapy	1 (2.8)
Bone marrow transplantation	2 (5.6)
Hydroxyuraea	2 (5.6)
Azacitidine	2 (5.6)
Chelation	0 (0.0)
MDS subtype*	
RA	8 (22.2)†
RARS	3 (8.3)
RCMD	11 (30.6)
RAEB	6 (16.7)
MDS-U	8 (22.2)
AML transformation	
Yes	7 (19.4)
No	29 (80.6)
Mortality	
Yes	9 (25.0)
No	27 (75.0)

ANC = absolute neutrophil count; MDS = myelodysplastic syndromes; RA = refractory anaemia; RARS = refractory anaemia with ringed sideroblasts; RCMD = refractory cytopaenia with multilineage dysplasia; RAEB = refractory anaemia with excess blasts; U = unclassified; AML = acute myeloid leukaemia.

**Defined as per the criteria of the World Health Organization.[23]*

†Including one case of MDS associated with an isolated del(5q) abnormality.

in Indian population has been reported to vary from 37.5–88%.[13] In addition, the frequency of chromosomal abnormalities varies between 37–50% in China, Thailand, Hong Kong and Japan.[13,14] Complex aberrations have been more frequently observed in Indian patients as compared to those from other Asian countries.[13]

As such, ethnic and/or geographical differences could be heterogeneous and contribute to clinical, cytogenetic or molecular events leading to MDS. Available reports on the incidence of MDS mostly originate from European countries, although major studies have been conducted in Japan.[15–22] To the best of the authors' knowledge, this is the first report detailing the cytogenetic profile of Omani patients with MDS. In order to analyse ethno-geographical differences in the pathogenesis of MDS, the current article aimed to compare the cytogenetic findings of Omani patients with *de novo* MDS with available data from Europe, North and South America, Africa and other Asian countries.

Methods

Data were collected from all patients with MDS presenting between 2006–2013 to the Department of Haematology at the Sultan Qaboos University Hospital (SQUH), a tertiary care centre in Muscat, Oman. A diagnosis of MDS was made as per the criteria of the World Health Organization (WHO).[23] Patients who did not fulfill the WHO criteria were excluded. All eligible subjects subsequently had their peripheral blood count recorded. In addition, bone marrow samples were obtained prior to the initiation of any therapy.

Cytogenetic analysis of the bone marrow samples was performed using GTG banding, with karyotypes reported according to the International System for Human Cytogenomic Nomenclature.[24] At least 20 metaphases were karyotyped and analysed from 24- and 48-hour bone marrow cultures. Clonal

Table 2: Age/gender distribution across subtypes of Omani patients with myelodysplastic syndromes presenting to the Sultan Qaboos University Hospital, Muscat, Oman (N = 36)

MDS subtype*	n (%)						
	Total	Age in years				Gender	
		0–20	21–40	41–60	>60	Male	Female
RA	8 (22.2)	0 (0.0)	0 (0.0)	2 (5.4)	6 (16.7)	3 (8.3)	5 (13.9)
RARS	3 (8.3)	0 (0.0)	0 (0.0)	1 (2.8)	2 (5.6)	3 (8.3)	0 (0.0)
RCMD	11 (30.6)	0 (0.0)	1 (2.7)	4 (11.1)	6 (16.7)	5 (13.9)	6 (16.7)
RAEB	6 (16.7)	1 (2.8)	0 (0.0)	2 (5.6)	3 (8.3)	3 (8.3)	3 (8.3)
MDS-U	8 (22.2)	0 (0.0)	1 (2.7)	1 (2.8)	6 (16.7)	4 (11.1)	4 (11.1)
Total	**36 (100.0)**	**1 (2.8)**	**2 (5.6)**	**10 (27.8)**	**23 (63.9)**	**18 (50.0)**	**18 (50.0)**

MDS = myelodysplastic syndromes; RA = refractory anaemia; RARS = refractory anaemia with ringed sideroblasts; RCMD = refractory cytopaenia with multilineage dysplasia; RAEB = refractory anaemia with excess blasts; U = unclassified.

**Defined as per the criteria of the World Health Organization.[23]*

Table 3: Cytogenetic prognosis of Omani patients with myelodysplastic syndromes presenting to the Sultan Qaboos University Hospital, Muscat, Oman (N = 36)

Cytogenetic prognosis*	Cytogenetic abnormality	n (%)					
		Total†	MDS subtype				
			RA	RARS	RCMD	RAEB	MDS-U‡
Very good	-Y	1 (2.8)	-	-	-	-	1 (2.8)
Good	Normal	23 (63.9)	6 (16.7)	2 (5.6)	8 (22.2)	4 (11.1)	3 (8.3)
	del(5q)	1 (2.8)	1 (2.7)	-	-	-	-
	del(12p)	0 (0.0)	-	-	-	-	-
	del(20q)	0 (0.0)	-	-	-	-	-
Intermediate (all single/double abnormalities)	del(7q)	0 (0.0)	-	-	-	-	-
	+8	2 (5.6)	1 (2.8)	-	-	1 (2.8)	1 (2.8)
	i(17)(q10)	1 (2.8)	-	-	-	-	1 (2.8)
	+19	0 (0.0)	-	-	-	-	-
	+21	1 (2.8)	1 (2.8)	-	-	-	-
Poor (including double abnormalities)	inv(3)	0 (0.0)	-	-	-	-	-
	t(3q)	0 (0.0)	-	-	-	-	-
	del(3q)	0 (0.0)	-	-	-	-	-
Very poor	Complex	1 (2.8)	-	-	-	1 (2.8)	-

MDS = myelodysplastic syndromes; RA = refractory anaemia; RARS = refractory anaemia with ringed sideroblasts; RCMD = refractory cytopaenia with multilineage dysplasia; RAEB = refractory anaemia with excess blasts; U = unclassified.

**As per the Revised International Prognostic Scoring System.[25]*

†The total dataset does not add up to 36 as some patients may have had more than one abnormality.

‡Including two cases of MDS-U with a del(18p) abnormality and one other abnormality.

abnormalities were defined as two or more cells with the same whole chromosome gain/chromosome rearrangement or three or more cells with the same chromosome loss. A complex karyotype was defined as three or more cytogenetic abnormalities.

Ethical approval for this research was received from the Research & Ethics Committee of the College of Medicine & Health Sciences, Sultan Qaboos University (MREC #896).

Table 4: Abnormal karyotypes among Omani patients with myelodysplastic syndromes presenting to the Sultan Qaboos University Hospital, Muscat, Oman (N = 36)

Patient	Age/gender	MDS subtype*	Karyotype	Survival in months
1	69/M	MDS-U	45,X,-Y[17]/46,XY[3]	18
2	67/F	MDS-U	46,XX,del(18)(p11)[20]	5
3	67/F	RAEB	46,XX,add(1)(q42) del(13)(q31)[13]/46,XX[7]	16
4	78/F	RCUD	47,XX,+21[17]/46,XX[1]	4
5	68/F	MDS-U	47,XX,+8[9]/46,XX[11]	7
6	64/F	RA	46,XX,del(5)(q15q31),del(11)(q23)[8]/46,XX[6]	5
7	58/F	RAEB	51,XX,+1,+8,+10,+i(11)(q10),+13[18]	3
8	67/M	MDS-U	46,XY,i(17)(q10)[4]/46,XY[27]	15

MDS = myelodysplastic syndromes; M = male; U = unclassified; F = female; RAEB = refractory anaemia with excess blasts; RCUD = refractory cytopaenia with unilineage dysplasia; RA = refractory anaemia.

**Defined as per the criteria of the World Health Organization.[23]*

Cytogenetic and Patient Data from Oman

A total of 36 Omani patients with MDS were successfully karyotyped. Of these, eight patients had refractory anaemia (RA; 22.2%), three had RA with ringed siderolasts (8.3%), 11 had refractory cytopaenia with multilineage dysplasia (30.6%), six had RA with excess blasts (16.7%) and eight had unclassified MDS (22.2%). One of the patients with RA with ringed siderolasts had MDS associated with an isolated del(5q) abnormality. Cytopaenia with bilineage was observed in 15 patients (41.7%), while cytopaenia with trilineage was seen in 13 patients (36.1%). Most of the patients (75.0%) had <5% bone marrow blasts. A total of 29 patients received supportive therapy only (80.6%). Seven patients had AML transformation (19.4%). The mortality rate was 25.0%. There was an equal number of male and female patients and the majority of the patients were over 60 years old (63.9%) [Table 1]. The median follow-up period was 28 months (range: 3–70 months). Table 2 shows the distribution of MDS subtypes according to age and gender.

Overall, 26 patients (72.2%) had normal karyotypes which indicated a good prognosis according to the Revised International Prognostic Scoring System (IPSS-R) [Table 3].[25] One patient had a normal variant and another had a non-clonal abnormality. Eight patients had abnormal karyotypes (22.2%), of which two patients had clones which had trisomy 8 and one patient each had trisomy 21, a del(5)(q15q31) abnormality, a del(11)(q23) abnormality, an i(17)(q10) abnormality, a del(18)(p11) abnormality and an absent Y chromosome [Table 4]. Six of these eight patients also showed normal clones along with abnormal clones.

Comparison of Omani Data with Other Populations

The characteristics of Omani patients with MDS were compared to those previously reported from other populations [Table 5].[3,7,11,13,15,16,22,26–33] The median age of patients with MDS in Oman (65 years old) was lower than that reported from Europe (65–74 years old) but was higher compared to other Asian countries (50–60 years old).[10,13,15,17,19–22,26,28,31] The median age of the patients in Tunisia was 60 years old.[22] Brazilian patients had the youngest median age (29 years old).[27] Among Omani patients, the male-to-female ratio was 1:1, which was in accordance with a sample from Thailand and close to ratios reported from Brazil (1.2:1) and Germany (1.3:1);[3,26,27] however, this finding was contrary to many other Asian countries and certain European, North American and African countries in which males outnumbered females.[7,11,13,15,22,28,30,31] Further research is needed to determine a possible cause for this gender difference between populations.

The majority of Omani patients showed normal karyotypes (62.2%) and were believed to have a good prognosis according to IPSS-R classifications.[25] Only published data on the frequency of abnormal karyotypes from Japan (23.9%) and China (37.1%) were close to the data from Oman.[16,28] Chromosomal abnormalities such as i(17q), trisomy 21 and the absence of the Y chromosome were seen in one each of the Omani patients (2.8% each). Studies from Germany, Japan and Argentina also reported patients with loss of the Y chromosome (7.0%, 1.1% and 2.7%, respectively);[3,15,29] however, this abnormality was not observed among patients from Thailand, Switzerland or Brazil.[7,26,27] Similarly, trisomy 21 was not observed

Table 5: Literature review and comparison of the cytogenetic marker profiles of patients with myelodysplastic syndromes[3,7,11,13,15,16,22,26–33]

Region	Africa	NA	South America		Europe				Asia						
Country	**Tunisia**	**USA**	**Argentina**	**Brazil**	**Germany**	**Italy**	**Spain**	**Switzerland**	**India**	**China**	**Korea**	**Taiwan**	**Thailand**	**Japan**	**Oman**
Author and year of study	Gmidène *et al.*[22] (2008)	Jacobs *et al.*[11] (1986)	Belli *et al.*[29] (2012)	Borgonovo *et al.*[27] (2005)	Haase *et al.*[3] (2005)	Bernasconi *et al.*[32] (2007)	Solé *et al.*[33] (2005)	Parlier *et al.*[7] (1994)	Dakshinamurthy *et al.*[13] (2005)	Zhao *et al.*[28] (2002)	Lee *et al.*[31] (1999)	Tien *et al.*[30] (1994)	Intragumtornchai *et al.*[26] (1998)	Oguma *et al.*[15] (1995)	Present research
Total subjects	224	49	518	93	2,124	491	968	109	52	128	149	68	117	838	36
Median age in years	60	62	69	29	66	65	70	69[§]	55	50	53	59	56	60	65
Male-to-female ratio	1.4:1	1.3:1	1.4:1	1.2:1	1.3:1	1.5:1	1.3:1	1.5:1	1.7:1	1.6:1	1.9:1	1.9:1	1.1	1.7:1	1:1
Patients with abnormal karyotypes, n (%)															
Overall	114 (50.9)	19 (38.8)	222 (42.9)	64 (68.8)	1,080 (50.8)	294 (59.9)	454 (46.9)	61 (56.0)	31 (59.6)	42 (32.8)	-	34 (50.0)	15 (12.8)	200 (23.9)[¶]	8 (22.2)
del5q/-5	30 (13.4)	3 (6.1)	19 (3.7)*	(12.5)[†]	71 (11.9)[‡]	43 (8.8)	55 (5.7)	37 (33.9)	13 (25.0)	6 (4.7)	-	5 (7.4)	3 (2.6)	8 (1.0)[¶]	1 (2.8)
del7q/-7	17 (7.6)	2 (4.0)	15 (2.9)*	(14.1)[†]	446 (20.9)	33 (6.7)	43 (4.4)	16 (14.7)	10 (19.2)	2 (1.6)	-	11 (16.2)	4 (3.4)	9 (1.1)[¶]	-
Trisomy 8	7 (3.1)	5 (10.2)	26 (5.0)*	(9.4)[†]	339 (16.0)	22 (4.5)	56 (5.8)	16 (14.7)	6 (11.5)	8 (6.3)	-	7 (10.3)	4 (3.4)	15 (1.8)[¶]	3 (8.3)
del(20q)	7 (3.1)	3 (6.1)	14 (2.7)*	(7.8)[†]	19 (0.9)	15 (3.1)	13 (1.3)	14 (12.8)	6 (11.5)	1 (0.8)	-	3 (4.4)	1 (0.9)	16 (1.9)[¶]	-
i(17q)	2 (0.9)	-	-	-	-	-	10 (1.0)	-	1 (1.9)	-	-	-	-	-	1 (2.8)
Trisomy 21	1 (0.4)	-	1 (0.2)*	(7.8)[†]	-	-	8 (0.8)	-	-	-	-	-	-	-	1 (2.8)
-Y	1 (0.4)	-	14 (2.7)*	-	148 (7.0)	5 (1.0)	17 (1.8)	-	1 (1.9)	1 (0.8)	-	-	-	9 (1.1)[¶]	1 (2.8)
AML transformation, n (%)	-	11 (22.4)	111 (21.4)	-	-	132 (26.9)	218 (22.5)	-	10 (19.2)	50 (39.1)	25 (16.8)	20 (29.4)	29 (24.8)	-	7 (19.4)

NA = North America; AML = acute myeloid leukaemia.

**Fragment of antibody subtype-classified population. †Percentages out of the total number of MDS cases with abnormal karyotypes. No exact values were provided in the original publication. ‡5q-syndrome as per the World Health Organization classifications (available in 595 patients).[23] §Mean age. ¶Data for these categories sourced from: Shimizu H, Matsushita Y, Aoki K, Nomura T, Yoshida Y, Mizoguchi H. Prevalence of the myelodysplastic syndromes in Japan.[16w]*

in Thailand or India.[13,26] The USA had the lowest percentage of AML transformation (2.8%), followed by Korea (16.8%) and Oman (19.4%).[31]

The overall percentage of abnormal karyotypes was lower among Omanis compared to other populations (22.2% versus 23.9–68.8%), although this may be due to the low number of patients included in the Omani sample.[3,7,11,13,15,16,22,26–33] The highest percentage of patients with abnormal karyotypes was reported from Brazil.[27] The frequency of cytogenetic abnormalities according to MDS subtype was found to be different among Omani patients when compared to other populations, with most Omani patients having normal karyotypes and thus a good prognosis.[3,7,11,13,15,16,22,26–33]

The current research sought to compare the cytogenetic characteristics of Omani patients with MDS to those reported among other geographic/ethnic populations. A review of the literature revealed that this dataset constitutes the first report from an ethnic Omani population. However, verification of the findings of this research is needed with a larger sample. As the native Omani population is relatively small, numbering approximately 2.35 million in 2015, the number of patients with MDS presenting to SQUH was hence limited and the sample size too small to draw statistically significant conclusions.[34] As such, it is recommended that the sample size be increased in future studies. Socioeconomic characteristics and access to the healthcare system may also contribute to MDS awareness and detection rates within a given population. The referral of suspected patients from rural healthcare centres to tertiary hospitals for cytogenetic testing could also increase the detection/confirmation of MDS markers for better characterisation.

Conclusion

To the best of the authors' knowledge, this report is the first from an Omani population detailing the cytogenetic characteristics of patients with MDS. These data may serve as a basis for further research in Oman and a comparison with other populations.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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