Rheumatic and Autoimmune Diseases May Have a Role in Disease Progression of Myelodysplastic Syndrome

Romatolojik ve Otoimmün Hastalıkların Myelodisplastik Sendromun Progresyonunda Rolü Olabilir

Salih KOZAN, MD, Msc,[a]
Deniz TORUN, MD, Msc,[a]
Yusuf TUNCA, MD, Prof.,[a]
Cengiz BEYAN, MD, Prof.,[b]
Ahmet İFRAN, MD, Assoc.Prof.,[b]
M. Kürşat KAPTAN, MD, Assoc.Prof.,[b]
Ali Uğur URAL, MD, Prof.,[b]
Oral NEVRUZ, MD, Assoc.Prof.,[b]
Ferit AVCU, MD, Assoc.Prof.,[b]
A. Türker ÇETİN, MD, Prof.,[b]
Ahmet Emin KÜREKÇİ, MD, Prof.,[c]
Davut GÜL, MD, Prof.,[a]
Yunus Kasım TERZİ, MD,[d]
Zehra Dilşad ÇOBAN, MD,[d]
Muhterem BAHÇE, MD, Prof.,[a]
Şefik GÜRAN, MD, Prof.[d]

Departments of
[a]Medical Genetics,
[b]Haemataology,
[c]Pediatric Hematology,
[d]Medical Biology
Gülhane Military Medical Academy,
Ankara

Geliş Tarihi/*Received:* 08.04.2011
Kabul Tarihi/*Accepted:* 02.02.2012

Yazışma Adresi/*Correspondence:*
Şefik GÜRAN, MD, Prof.
Gülhane Military Medical Academy,
Department of Medical Biology, Ankara,
TÜRKİYE/TURKEY
sefguran@yahoo.com

doi: 10.5336/medsci.2011-24201

ABSTRACT Objective: Myelodysplastic syndrome (MDS) is a clonal bone marrow disorder that leads to underproduction of normal blood cells. It causes dysgenesis of the blood cells. The cause of de novo MDS is not known. About 10% of cases of MDS are secondary, most often due to radiation treatment or chemotherapy for cancer. The role of other diseases observed in the patients and their families is not clear in the progression of MDS. Here, the diseases observed in our series (71 MDS cases and their families) were compared with the normal controls (71 normal cases and their families) to understand the affect of other diseases in the progression of MDS. **Material and Methods:** Among 71 MDS cases, 29 cases with refractory cytopenia with unilineage dysplasia, one cases with refractory anemia with ring sideroblast, 28 cases with refractory cytopenias with multilineage dysplasia, 11 cases with refractory anemia with excess blasts and 2 cases with MDS associated with isolated del (5q) were diagnosed with clinical and laboratory results. The diseases in MDS and the control groups were classified according to general classifications. **Results:** The numbers of affected patients in each group represented no significant difference between MDS and the control groups. According to these results, no correlation was found between the other diseases and MDS group. As known, some diseases have an accumulation in some families representing genetic predisposition. In order to find out the role of such systemic diseases frequently observed in one family, two groups were compared. In this group, the families which had two or more affected cases with the same diagnoses were accounted. Twenty six families had similar two or more diseases in MDS group whereas 21 families had similar two or more diseases in the control group. The difference between the MDS group (8 families) and the control group (2 families) which had rheumatic and autoimmune diseases were noticed. The number of affected families in MDS group with rheumatic and autoimmune diseases was greater than the number of affected families in the control group ($p = 0.049$). **Conclusion:** Our results may represent the possible role of rheumatic and autoimmune diseases in MDS etiology. Further findings are needed which represent the predisposition of rheumatic and autoimmune conditions in MDS progression.

Key Words: Myelodysplastic syndromes; rheumatic diseases; autoimmune diseases; cytogenetics; genetic predisposition to disease

ÖZET Amaç: Myelodisplastik sendrom (MDS) normal kan hücrelerinin azalmış üretimine yol açan kolonal bir kemik iliği hastalığıdır. Kan hücrelerinin disgenezisine neden olur. De novo MDS'nin nedeni bilinmemektedir. MDS olgularının %10 kadarı en sık kanser için radyasyon tedavisi veya kemoterapiye bağlıdır. Hastalarda ve ailelerinde gözlenen diğer hastalıkların MDS progresyonundaki rolü açık değildir. Burada diğer hastalıkların MDS progresyonundaki etkisini anlamak için serimizde (71 MDS olgusu ve aileleri) gözlenen hastalıklar normal kontrollerle (71 normal olgu ve aileleri) karşılaştırıldı. **Gereç ve Yöntemler:** Yetmiş bir MDS hastasından; 29'una tek dizeli displazili refrakter sitopeni, birine halka sideroblastlı refrakter anemi, 28'ine çok dizeli displazili refrakter sitopeni, 11'ine aşırı blastlı refrakter anemi, 2'sine izole del (5q) ile ilişkili MDS tanısı konuldu. MDS grubundaki ve kontrol grubundaki hastalıklar genel sınıflandırmalara göre sınıflandırıldı. **Bulgular:** Her gruptaki etkilenen hasta sayısı MDS ve kontrol grubunda önemli fark göstermedi. Bu sonuçlara göre diğer hastalıklarla MDS grubu arasında korelasyon bulunmadı. Bilindiği gibi, bazı hastalıklar genetik yatkınlığı olan bazı ailelerde birikim gösterir. Bir ailede sıklıkla gözlenen böyle sistemik hastalıkların rolünü bulmak için iki grup karşılaştırıldı. Bu grupta aynı tanıyı almış iki veya daha fazla olgunun olduğu aileler değerlendirildi. MDS grubunda 26 ailede iki veya daha fazla benzer hastalık vardı, oysa kontrol grubunda 21 ailede iki veya daha fazla benzer hastalık vardı. Romatolojik ve otoimmün hastalıkları olan MDS grubu (8 aile) ile kontrol grubu (2 aile) arasındaki fark bildirildi. MDS grubundaki romatizmal ve otoimmün hastalığı olan etkilenen aile sayısı kontrol grubundaki etkilenen aile sayısından daha yüksek bulundu ($p=0,049$). **Sonuç:** Sonuçlarımız MDS etyolojisinde romatizmal ve otoimmün hastalıkların olası rolünü gösterebilir. MDS progresyonunda romatizmal ve otoimmün hastalıkların yatkınlığını gösteren daha fazla bulguya ihtiyaç vardır.

Anahtar Kelimeler: Myelodisplastik sendromlar; romatizmal hastalıklar; otoimmün hastalıklar; sitogenetik; hastalığa genetik yatkınlık

Turkiye Klinikleri J Med Sci 2012;32(4):910-6

The myelodysplastic syndromes are a heterogeneous group of disorders characterized by ineffective hematopoiesis, impaired maturation of hematopoietic cells, progressive cytopenias, and dysplastic changes in the bone marrow. MDS is a common malignancy of adults with an incidence of 50 cases per million in people over the age of 60 years. MDS is characterized by the accumulation of genetic damage, progression to marrow failure, and a high probability of developing acute myeloid leukemia (AML) (MDS/AML transformation).[1,2] About 90% of cases have no known etiologic cause (de novo MDS). Probably both genetic and environmental factors play a role. Secondary MDS (sMDS) generally occurs due to radiation treatment or chemotherapy (particularly alkylating agents and topoisomerase inhibitors) for cancer. Immunosupressive therapy is related with sMDS or therapy-related MDS. Occupational exposure to radiation, benzene or other organic solvents may be the cause of MDS in some cases. Congenital conditions such as Down syndrome, Fanconi anemia, and Bloom syndrome are also associated with MDS. MDS cases at an earlier age, suggest a "multiple-hit" mechanism of cancer development with genetic and environmental factors.[3,4] In recent years, large series were analyzed due to risk factors of MDS progression. Rheumatoid arthritis and pernicious anemia were found as the risk factors for MDS and AML. Systemic lupus erythematosus, polymyalgia rheumatica, autoimmune hemolytic anemia, systemic vasculitis and ulcerative colitis were found as risk factors in AML.[5]

Here, patient/family histories of 71 MDS and 71 normal cases were analyzed on the *pedigrees*. The co-existence of MDS and other diseases which may have a genetic predisposition in the families were tried to clarify. The results obtained from the families of MDS cases were compared with the results obtained from the control families.

MATERIAL AND METHODS

Here, we presented 71 MDS and MDS/AML transformed patients, presented between 2003-2010 with clinical and laboratory results including cytogenetic / molecular genetic findings (Table 1). The diagnosis and classification were done according to World Health Organization (WHO) 2008 criteria.[6] Detailed pedigree analyses were performed for 71 MDS and 71 control cases. The cases in control group were age-and sex-matched with the patients. The MDS patients were referred to our hospital from all geographical regions of Turkey. The control group was also selected from the similar regions of Turkey. In the first part of analysis, all the diseases observed in each family were counted. The results were grouped according to general classifications of the diseases.[7,8] In each *pedigree*, at least 15 patients were tried to be analyzed in three generations. In MDS group, a total of 1423 cases were analyzed for other diseases. Similarly 1346 cases were analyzed in the control group.

As known, genetic predisposition causes an accumulation of the same disease in the same family.[9] In order to find out the role of such systemic diseases frequently observed in one family, two groups were compared. In this group, the families which had two or more affected cases with the same diagnoses were accounted. All the disorders in patients and control families were noted. In order to find the role of genetically predisposed diseases on MDS progression, only the families with the frequently seen diseases were counted. The p value of every statistical data was evaluated according to chi square test. If one or two of the cells in contingency table had numbers less than 5, Fisher's Exact Test was used in statistical analysis.

RESULTS

Among 71 MDS patients, 51 cases were males and 20 cases were famales. The minumum age was 12 and the maximum age was 85 years. The median age was 53 years. According to clinical and laboratuary findings, 29 cases were diagnosed with refractory cytopenias with unilineage dysplasia (RCUD) (45.07%). One case was diagnosed with refractory anemia with ring sideroblasts RARS (1.40%). Twenty eight cases were diagnosed with refractory cytopenias with multilineage dysplasia RCMD (%39.44). Eleven cases were diagnosed with refractory anemia with excess blasts RAEB

TABLE 1: The clinical and laboratory findings of 71 MDS patients including family histories.

Diagnosis	Case Number/ Percentage	Male/Female Median age	Age	Sex	Other disorders in patient history	Other disorders in family history	Cytogenetic and molecular genetic abnormalities
RCUD	29 (40.84%)	20/9 62.93	40	M	Rheumatoidartritis, Therapy of rheumatoidartritis, Osteomyelitis, Anemia (Fe insufficiency)	Rheumatoid arthritis in one patients	-
			45	M	Chronic gyngival infection history	-	-
			78	F	Atherosklerosis (Miyocard infarction history)	-	+
			76	M	-	-	+
			-	-	-	-	Normal karyotype (25 cases)
RARS	1 (1.41%)	1/-74	74	M	-	-	-
RCMD	28 (39.44%)	19/9 48.12	72	F	-	-	+
			31	M	Psoriasis	Psoriasis in one patient	-
			28	M	Sjogren syndrome	Rheumatoid arthritis in one patient	-
			76	M	Rheumatoid arthritis Therapy related MDS	Rheumatoid arthritis in one patient	-
			79	M	-	Rheumatoid arthritis in two patients	-
			25	F	Portal vein thrombosis	-	-
			37	F	-	-	-
			51	F	-	-	-
			37	M	-	-	-
			62	M	-	-	+
			85	M	-	-	+
			21	M	-	-	+
			78	M	-	-	+
			24	M	-	-	+
							Normal karyotype (15 cases)
RAEB1	7 (9.86%)	6/1 33.28	19	M	-	-	-
			20	M	Hepatosplenomegaly	-	-
			21	M	-	-	+
			20	M	-	-	+
			62	F	-	-	+
			63	F	Scleroderma	Scleroderma in one patient	+
			60	F	Rheumatoid arthritis history Therapy of rheumatoid arthritis	Rheumatoidartritis history	+
			83	F	Rheumatoid artritis history Therapy of rheumatoid artritis	-	+

Contunied→

TABLE 1: *continued.*

			56	F	-	-	+	
			30	M	Rheumatological complaints in patient.	Rheumatoid arthritis diagnosis	-	
		3/1			No diagnosis.	in two relatives in his family		
RAEB2	4 (5.63%)	55.75	67	M	-	-	+	
			70	M	Prostate cancer	-	+	
					(surgical operation+ hormone therapy)			
Del(5q)	2 (2.82%)	2/-35.00	20	M	-	-	+	
			50	M	-	-	+	
RCC	-	-	-	-	-	-	-	
MDS U	-	-	-	-	-	-	-	

(Only the patients who had two or more rheumatic and autoimmune conditions in their families were noted) [The classifications were done according to World Health Organization (WHO) 2008 criteria.[6]
RCUD (Refractory cytopenias with unilineage dysplasia)
RARS (Refractory anemia with ring sideroblasts)
RCMD (Refractory cytopenias with multilineage dysplasia)
RAEB (Refractory anemia with excess blasts)
Del (5q) (MDS associated with isolated del (5q)
RCC (Childhood MDS, including refractory cytopenias of childhood)
MDS-U (MDS, unclassifiable)

(15.49%) [9 cases were type 1 (9.85%), 4 cases were type 2 (5.63%)], 2 cases were diagnosed with MDS associated with isolated del (5q) (2.82%) (Table 1).[6]

Nineteen (26.76%) patients revealed different cytogenetic abnormalities in their cytogenetic analyses. Eight patients (11.27%) had a complex karyotype (with 3 or more chromosomal abnormalities). Four cases had -Y (5.63%) and two cases had del 5q (2.81%) abnormalities (Table 1). In MDS group, 1423 cases were tried to be analyzed for other diseases. These results were compared with the data of 1346 cases analyzed in normal control families (Figure 1). The statistical analyses of these results are presented in Table 2. According to these results, all p values greater than 0.05 represented no correlation between MDS and normal control groups with respect to diseases observed in their families (Figure 1 and Table 2).

In order to find out the role of genetic predisposition of the other diseases, a criterion (two or more patients in the same family with the same diagnoses) was accepted. The family numbers of MDS group and control group were correlated according to these findings (Figure 2). Among the disease groups, the rheumatic and autoimmune conditions were found lower than 0.05 (p=0.049) as seen in Table 3. This correlation in MDS group and normal control group may represent a possible role of rheumatic and autoimmune diseases in MDS progression. In MDS group, eight families had two or more affected patients in the same family including rheumatoid arthritis (RA), scleroderma, psoriasis, Sjogren syndrome whereas in control group only two families had two and more affected patients including RA, and Hashimoto thyroiditis (Figure 2). In other disease groups, no correlation was observed between MDS group and normal control group (Table 3).

DISCUSSION

The MDSs are a clinically heterogeneous group of hematologic disorders with differing biology and clinical manifestations. They commonly have a clonal origin, dysplastic cellular morphology, abnormalities of cellular maturation, increased propensity to develop acute leukemia (20%-40%),

TABLE 2: The contingency tables and p values of the MDS patient data in Figure 1.

Disease Group	Data: contingency table (MDS group)			Probability (p-value)
		a	b	
a.	1	25	26	0.732
	2	1398	1320	
b.	1	3	2	1.000
	2	1420	1344	
c.	1	11	9	0.746
	2	1412	1337	
d.	1	36	33	0.895
	2	1387	1313	
e.	1	3	2	1.000
	2	1420	1344	
f.	1	2	3	0.679
	2	1421	1343	
g.	1	9	11	0.568
	2	1412	1335	
h.	1	2	2	1.000
	2	1421	1344	
ı.	1	3	2	1.000
	2	1420	1344	
k.	1	25	24	0.958
	2	1398	1322	
m.	1	1	2	0.615
	2	1422	1344	
n.	1	22	21	0.939
	2	1421	1325	
o.	1	5	6	0.693
	2	1418	1340	
p	1	3	2	1.000
	2	1420	1344	
r.	1	6	5	0.834
	2	1417	1341	
s.	1	1	2	0.615
	2	1422	1344	

(As seen, all disease groups had p values greater than 0.05).

ported as 10-20% in RCUD, 3-11% in RARS, 30% in RCMD, 40% in REAB, <1% in childhood MDS (RCC), uncommon in MDS associated with isolated deletion 5q [Del (5q)], very rare in MDS unclassifiable (MDS-U).[6] In our series, the rates of RCUD, RARS, RCMD, RAEB, Del (5q) were detected as 45.07%, 1.40%, 35.21%, 15.48%, 2.81%, respectively (Table 1).

Cytogenetic studies are important for patients with these disorders because the results can provide both diagnostic and prognostic information. A chromosomally abnormal clone can be detected in 40% to 60% of patients with de novo MDS and in approximately 90% of patients with therapy-related MDS.[1] Here, 18 cases had (25.35%) different cytogenetic abnormalities (Table 1). Our chromosomal abnormality percentage is smaller than the ones reported in the literature. This controversy may be explained by the high percentage of RCUD and the low percentage of RAEB in our series (Table 1).[10,11]

In recent years, some manuscripts described a higher risk of myeloid malignancies in autoimmune conditions such as in lymphoproliferative malignancies.[12,13] Anderson et al. analyzed the risk of autoimmune diseases in 13,486 myeloid malignancy patients (aged 67+ years) and 160,086 population-based controls. In this manuscript, MDS was found to associate with autoimmune conditions [Overall increased risk of AML (OR 1.29) and MDS (OR 1.50)]. Specifically, AML was associated with rheumatoid arthritis (RA) (OR 1.28), systemic lupus erythematosus (SLE) (OR 1.92), polymyalgia rheumatica (OR 1.73), autoimmune hemolytic anemia (OR 3.74), systemic vasculitis (OR 6.23), ulcerative colitis (OR 1.72) and pernicious anaemia (OR 1.57). MDS was associated with RA (OR 1.52) and pernicious anemia (OR 2.38).[12] In our series, we also found the coexistence of other diseases in each family. The number of diseases numbers in MDS group and normal control group represented larger p values (>0.05) as seen in Figure 1 and Table 2. These results indicated that the number of MDS cases in our series was not enough in number to have similar results obtained in the literature.

As known, some diseases have an accumulation in some families which represent genetic predisposition.[9] In order to find the role of such

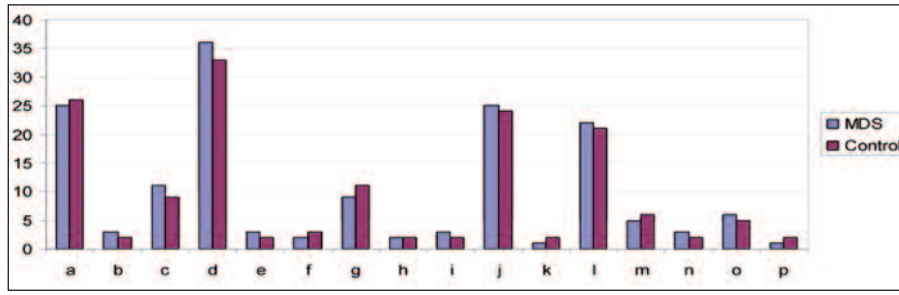

FIGURE 1: The total disease numbers, obtained from MDS groups and normal control groups.
a. Other malignancies; b. Genetic diseases; c. Psychiatric diseases; d. Cardiovascular diseases; e. Respirator diseases; f. Renal and genitourinary Diseases; g. Gastrointestinal diseases; h. Diseases of liver, Gall bladder, Bile ducts; i. Hematologic diseases; j. Endocrine diseases; k. Diseases of allergy and Clinical immunology; l. Rheumatic and autoimmune diseases; m. Infectious diseases; n. Neurologic disorders; o. Eye, ear, nose and throat diseases; p. Skin diseases;
(There were no patients in nutritional disease group and diseases of bone/mineral metabolism group in MDS and control families)
(See for colored from http://tipbilimleri.turkiyeklinikleri.com/)

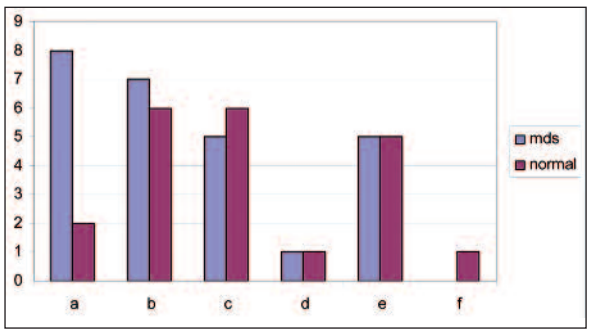

FIGURE 2: The family counts, with at least two affected cases in 71 MDS group and normal control group.
a. Rheumatic and autoimmune diseases; b. Cardiovascular disorders; c. Other malignancies; d. Genetic diseases; e. Endocrine diseases; f. Psychiatric diseases.
(See for colored from http://tipbilimleri.turkiyeklinikleri.com/)

TABLE 3: The contingency tables and chi-square and p value of the MDS group data and normal control group data in Figure 2.

Disease group	Data: contingency table (MDS group)			Probability (p-value)
		a	b	
a.	1	8	2	0.049
	2	63	69	
b.	1	7	6	0.771
	2	64	65	
c.	1	5	6	0.754
	2	66	65	
d.	1	1	1	1.000
	2	70	70	
e.	1	5	5	1.000
	2	66	66	
f.	1	0	1	1.000
	2	71	70	

(As seen, only group (a) which included rheumatic and autoimmune disease had a p value smaller than 0.05).

systemic diseases frequently observed in one family, two groups were compared. In this group, the families which had two or more affected cases with the same diagnoses were accounted. As seen, only group (a) which included rheumatic and autoimmune disease had a p value smaller than 0.05 (Figure 2 and Table 3). The number of affected families in MDS group with rheumatic and autoimmune diseases was found higher compared to the number of affected families in the control group. In other disease groups, all p values were greater than 0.05 (Figure 2 and Table 3). This result may be an evidence for need of further studies which may represent the predisposition of rheumatic and autoimmune conditions in MDS progression.[14]

REFERENCES

1. Orazi A, Czader MB. Myelodysplastic syndromes. Am J Clin Pathol 2009;132(2):290-305.
2. Bejar R, Ebert BL. The genetic basis of myelodysplastic syndromes. Hematol Oncol Clin North Am 2010;24(2):295-315.
3. Bernasconi P, Klersy C, Boni M, Cavigliano PM, Calatroni S, Giardini I, et al. World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with de novo primary myelodysplastic syndromes. Br J Haematol 2007;137(3):193-205.
4. Pişkin Ö. [Molecular pathogenesis of myelodysplastic syndrome]. Turkiye Klinikleri J Hem Onc-Special Topics 2009;2(2): 41-7.
5. Anderson LA, Pfeiffer RM, Landgren O, Gadalla S, Berndt SI, Engels EA. Risks of myeloid malignancies in patients with autoimmune conditions. Br J Cancer 2009;100(5):822-8.
6. Komrokji RS, Zhang L, Bennett JM. Myelodysplastic syndromes classification and risk stratification. Hematol Oncol Clin North Am 2010;24(2):443-57.
7. Mezzich JE. International surveys on the use of ICD-10 and related diagnostic systems. Psychopathology 2002;35(2-3):72-5.
8. Goldman L, Ausiello DA. Introduction. Cecil Medicine. 23rd ed. New York: Elsevier Publication; 2008. p.1-19.
9. Nussbaum RL, McInnes RR, Willard HF. Genetic counseling and risk assessment. Thompson and Thompson, Genetics in Medicine. 6th ed. Philadelphia: WB Saunders Company; 2001. p.375-89.
10. Bernasconi P, Alessandrino EP, Boni M, Bonfichi M, Morra E, Lazzarino M, et al. Karyotype in myelodysplastic syndromes: relations to morphology, clinical evolution, and survival. Am J Hematol 1994;46(4):270-7.
11. Cazzola M, Malcovati L. Prognostic classification and risk assessment in myelodysplastic syndromes. Hematol Oncol Clin North Am 2010;24(2):459-68.
12. Anderson LA, Pfeiffer RM, Landgren O, Gadalla S, Berndt SI, Engels EA. Risks of myeloid malignancies in patients with autoimmune conditions. Br J Cancer 2009;100(5): 822-8.
13. Löfström B, Backlin C, Sundström C, Hellström-Lindberg E, Ekbom A, Lundberg IE. Myeloid leukaemia in systemic lupus erythematosus--a nested case-control study based on Swedish registers. Rheumatology (Oxford) 2009;48(10):1222-6.
14. Çetin M, Koçyiğit İ. [Myelodysplastic syndromes]. Turkiye Klinikleri J Int Med Sci 2007;3(2):90-5.