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STRUCTURAL ABERRATIONS OF 1p36 IN HEMATOLOGIC MALIGNANCIES*

HEMATOLOJİK KANSERLERDE 1p36'NIN YAPISAL ANOMALİLERİ

Rahiye Dilhan KURU[1], Ayşe ÇIRAKOĞLU[1], Şükriye YILMAZ[1], Şeniz ÖNGÖREN[2], Muhlis Cem AR[2], Teoman SOYSAL[2], Ayhan DEVİREN[1], Yelda TARKAN ARGÜDEN[1]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Medical Biology, Istanbul, Turkiye
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Istanbul, Turkiye

ORCID IDs of the authors: R.D.K. 0000-0001-8088-5336; A.Ç. 0000-0003-0330-2277; Ş.Y. 0000-0001-8076-3080; Ş.Ö. 0000-0002-2809-5510; M.C.A. 0000-0002-0332-9253; T.S. 0000-0002-7417-2118; A.D. 0000-0003-2117-8230; Y.T.A. 0000-0002-5405-3365

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ABSTRACT

Objective: Structural aberrations of 1p36 are very common in most hematologic malignancies. 1p36 consists of genes that are important in oncogenesis. The aim of this study was to define 1p36 abnormalities and their distributions within different hematologic malignancies.

Materials and Methods: To achieve this goal, we retrospectively evaluated the cytogenetic results of our hematological cancer cases.

Result: We found deletions or rearrangements of breakpoint 1p36 in 18 patients with various hematologic malignancies, including myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), multiple myeloma (MM), chronic myeloid leukemia (CML), lymphoma, B cell acute lymphoblastic leukemia (B-ALL), idiopathic thrombocytopenic purpura (ITP) and aplastic anemia (AA). We observed t(1;3)(p36;p21) in one AML-M2 patient and t(1;3)(p36;q21) in two CML patients. Eight patients (1 MDS, 2 MM, 3 CML, 1 AML, and 1 AA) had translocations and rearrangements. One ITP patient had der(1)t(1;1)(p36;q21) and another CML patient had der(1)t(1;1)(p36;q12). We demonstrated several terminal deletions with different breakpoints between 1p11 and 1p36 in five patients, (2 MDS, 2 lymphomas, and 1 B cell acute lymphocytic leukemia).

Conclusion: The 1p36 breakpoint is a hot spot for cancer-related chromosome rearrangements and is associated with poor prognosis. In order to emphasize the importance of 1p36 in hematologic malignancies it essential to build a large data pool on the

ÖZET

Amaç: 1p36 bölgesinin yapı anomalileri bir çok hematolojik kanserde oldukça yaygındır. 1p36 bölgesi, kanser gelişiminde etkili olan önemli genlere sahiptir. Bu çalışmanın amacı, olgularımıza ait 1p36 anomalilerini ve farklı hematolojik kanserlerdeki dağılımlarını belirtmektir.

Gereç ve Yöntem: Bu çalışma için hematolojik kanser olgularımızın sitogenetik sonuçları retrospektif olarak değerlendirilmiştir.

Bulgular: Myelodisplastik sendrom (MDS), akut myeloid lösemi (AML), multipl myelom (MM), kronik myeloid lösemi (KML), lenfoma, B hücreli akut lenfoblastik lösemi (B-ALL), idyopatik trombositopenik purpura (ITP) ve aplastik anemi (AA) hastası olmak üzere 18 farklı hematolojik kanser olgusunda 1p36 kırık noktasına ait delesyon ya da yeniden düzenlenmeler saptanmıştır. Bir AML-M2 hastasında t(1;3)(p36;p21) ve iki KML hastasında t(1;3)(p36;q21) gözlemlenirken, sekiz hastada (1 MDS, 2 MM, 3 KML, 1 AML and 1 AA) translokasyon ve yeniden düzenlenmeler tespit edilmiştir. Bir ITP hastası der(1)t(1;1)(p36;q21) ve bir KML hastasında ise der(1)t(1;1)(p36;q12) kromozom yapısı saptanmıştır. Beş hastada (2 MDS, 2 lenfoma, ve 1 B hücreli akut lenfositik lösemi)1p11 ve 1p36 arasındaki farklı kırık noktalarında çeşitli terminal delesyonlar gözlenmiştir.

Sonuç: 1p36 kanserle ilişkili kromozom yeniden düzenlemeler için sıcak noktadır ve kötü prognozla ilişkilendirilmektedir. 1p36 bölgesinin hematolojik kanserlerdeki önemini vurgulamak için, konuyla ilgili geniş bir veri havuzu oluşturmak önemlidir. Serimiz-

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Corresponding author/İletişim kurulacak yazar: Rahiye Dilhan KURU – dilhank@iuc.edu

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subject. The distribution of breakpoints in 1p abnormalities in our series was remarkable, as 12 out of 18 1p breakpoints were 1p36. However, while 1p breakpoints aggregated on 1p36 in all translocations, there was only one 1p36 breakpoint in five deletions. With this paper, we contribute to the relevant literature by reporting our results.

Keywords: 1p36, leukemia, lymphoid malignancies, myeloid malignancies, cytogenetics, bone marrow

deki 1p36 anomalilerinin dağılımı, 18 hastanın 12'sinde 1p kırık noktasının 1p36 olması nedeniyle dikkat çekicidir. Ancak, bütün translokasyonların kırık noktaları 1p36'da yoğunlaşırken, beş delesyonun sadece birinde kırık noktası 1p36 idi. Bu çalışma ile sonuçlarımızı sunarak bu alandaki literatüre katkı sağlayacağımızı düşünmekteyiz.

Anahtar Kelimeler: 1p36, lösemi, lenfoid kanserler, myeloid kanserler, sitogenetik, kemik iliği

INTRODUCTION

Conventional cytogenetic testing is a major tool in the diagnosis, classification, and follow-up of hematologic malignancies. Structural aberrations of chromosome 1p36, including translocations, inversions, deletions, and duplications are common in several hematologic malignancies. These aberrations are mostly observed in myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), and multiple myeloma (MM) (1). Although rarely, 1p36 abnormalities may also be observed in acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and non-Hodgkin's lymphoma (NHL) (1-3). Furthermore, a shorter overall survival has been correlated with breaks in the 1p32–p36 region in malignancies (4-8). There are various reports on relevant genes such as *CDC2L1* and *CDC2L2* (cell division control 1 and 2), *PRDM16* (PR/SET domain 16), *TNFRSF14* (a member of the tumor necrosis factor receptor family), *DFFB* (DNA fragmentation factor subunit beta), *PRKCZ* (protein kinase C zeta), *MMP23* (metalloproteinase), SKI (sarcoma virus homolog), *ERRFI1* (a cell growth regulator) that are located on 1p (4,7,9-16). According to the literature, molecular mechanisms of these genes are involved in several different malignancies.

This study aims to determine the 1p36 abnormalities and their distribution across different hematologic malignancies. For this purpose, we retrospectively evaluated the cytogenetic results of our hematological cancer cases. We intend to contribute to the relevant literature by presenting the cytogenetic findings of 18 cases with various hematologic malignancies and different 1p abnormalities.

MATERIAL and METHODS

In this study, cytogenetic results of 5,098 hematologic cancer cases referred from IU-C, Cerrahpasa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, to the Cytogenetics Laboratory of the Medical Biology Department of Cerrahpasa Faculty of Medicine, IU-C, between 1994 and 2017 were evaluated retrospectively in terms of chromosome 1p abnormalities. Eighteen cases (12 males, six females) with a median age of 62.5 (range 31-86) constituted the study group. Distribution of the patients was as follows: chronic myeloid leukemia (CML, 6 cases), MDS (3 cases), acute myeloid leukemia (AML, 2 cases), MM (2 cases), lymphoma (2 cases; one with diffuse large B-cell lymphoma (DLBCL) and one with follicular non-Hodgkin's lymphoma, B-ALL (1 case), idiopathic thrombocytopenic purpura (ITP, 1 case) and aplastic anemia (AA, 1 case). Fifteen of these patients were newly diagnosed, and 3 (1 CML, 1AML, and 1AA) were follow-up patients. The study was approved by the institutional Medical Ethics Committee (Date: 03.07.2018, No: A-38).

Bone marrow (BM) and/or peripheral blood samples were used for conventional cytogenetic analyses. Cytogenetic analyses were performed with 24-h or 48-h unstimulated BM cultures, and 72-h peripheral blood cultures using standard procedures (17). Two cultures were set up for each patient by adding 0.1 ml of heparinized bone marrow aspiration material to 5 ml of medium for BM cultures. Similarly, two cultures were set up for each patient by adding 0.2 ml of heparinized peripheral blood to 5 ml of medium in a 72-hour culture.

After harvesting, the GTL (G-bands using trypsin and staining with Leishman) banding technique was applied to the slides, and karyotypes were described according to the An International System for Human Cytogenomic Nomenclature (ISCN), 2016 (18).

RESULTS

This study presents deletions and rearrangements of 1p in 18 patients with hematologic malignancies. The aberrations we observed include six additions (33%), five deletions (28%), four translocations (22%), two derivative chromosomes (11%), and one inversion (6%).

Additions were the most observed abnormalities with the accumulation of breakpoints at 1p36 in five cases. One AML, two CML, and two MM cases had add(1)(p36). The other chromosomal addition seen in our study was add(1)(p34) in a patient with AML.

Five patients had deletions with different breakpoints from 1p11 to 1p36. These deletions were del(1)(p35), and

del(1)(p11) in two MDS cases, del(1)(p32p36) in DLBCL, del(1)(p22) in ALL, and del(1)(p21) in follicular non-Hodgkin lymphoma.

We observed reciprocal translocations of 1p36 with other chromosomes in five patients. These translocations were: t(1;3)(p36;q21) in two patients with CML, t(1;3)(p36;p21) (previously reported (19)), in one patient with AML M2, t(1;2)(p36;q11) in one patient with MDS and, t(1;10)(p36;q21) in one patient with CML.

We identified derivative chromosomes 1 in two cases. One of them was der(1)t(1;1)(p36;q21) in an ITP case, and the other was der(1)(1qter→1q12::1p36→1qter) in a CML case.

Apart from these, we observed inv(1)(p36q41) in one patient with AA.

Finally, t(1;2)(p36;q11), t(1;10)(p36;q21), inv(1)(p36q41) and der(1)t(1;1)(p36;q21) were observed as sole abnormalities.

Characteristics, diagnoses, and karyotype formulas of our patients are shown in Table 1. The distribution of structural aberrations of chromosome 1p in our cases is presented in Table 2. The distribution of hematologic malignancies by breakpoints in chromosome 1 ideogram is demonstrated in Figure 1. The most commonly observed breakpoint was 1p36 in our study. It was detected in 12 cases, 6 of whom had CML while 2 had AML, 2 had MM, 1 had AA, and 1 had ITP. Examples of deletion and rearrangements at 1p36 are shown in Figure 2.

Table 1: Patient characteristics and karyotype formulas

Case	Age, years	Gender	Clinical diagnosis	Karyotype
1	35	F	AML M2	44~46,XX,t(1;3)(p36;p21)[21],-21[3],+mar1[3],+mar2[2][cp21]
2	57	F	MM	38~46,X,-X[6],add(1)(p16)[6],inv(11)(p15;q11)[3], add(19)(p or q13)[2],+mar1[6],+mar2[3][cp6]/46,XX[10]
3	70	M	MDS	46,XY,t(1;2)(p36;q11)[2]/46,XY[4]
4	55	F	CML	45~46,XX,der(1)(1qter→1q12::1p36→1qter),t(9;22)(q34;q11)[36] [cp36]/46~48,XX,t(9;22)(q34;q11)[4],+der(22)t(9;22)(q34;q11)[3], +mar[4][cp4]/46,XX,t(9;22)(q34;q11)[10]
5	51	M	CML	44~46,XY,t(1;10)(p36;q21)[cp4]/46,XY[10]
6	86	M	ITP	40~46,XYder(1)t(1;1)(p36;q21)[cp10]/46,XY[7]
7	80	M	CML	36~50,X,-Y[20],add(1)(p36)[17],del(2)(q21q23)[17], add(3)(p21)[17],-4[3],-5[3],add(5)(q22?)[5],del(6)(q13)[17],-7[3], add(8)(q23)[16],-10[6],del(11)(q23)[16],-13[16],add(15)(q25)[10], -18[5],-19[3],-20[3],-22[3],+r[3],+r[1],+mar1[17], +mar1[8],+mar1[1],+mar2[11],+mar2[3],+mar3[7], +mar4[4],+mar5[9],+mar6[3],+mar7[3],+mar8[2], +mar9[3],+mar10[5],+mar10[2],1~2dmins[3][cp26]/46,XY[10]
8	31	M	AA	46,XY,inv(1)(p36q41)[3]/46,XY[12]
9	55	F	AML recurrence	36~46,XX,add(1)(p34)[13],add(1)(p36)[11],-9 [3],der(9)t(9;?)(q?;?) [14],del(11)(q13)[24][cp24]/46,XX[2]
10	69	M	MM	49~51,Y,del(X)(q25)[4],add(1)(p36)[4],del(4)(q32)[4],+5[2], add(5)(p13)[2],+6[2],add(6)(q12)[4],add(7)(p22)[4], add(9)(q34)[4],add(10)(q25)[3],-13[4],i(15)(q10)[4],+mar1[4], +mar2[4],+mar3[4],+mar4[3][cp4]/46,XY[9]
11	76	F	CML	42~44,XX,t(1;3)(p36;q21)[17],-15[3][cp17]
12	66	M	CML	39~47,XY,add(1)(p36)[4],t(3;22)(q28;q11)[12], +der(22)t(3;22)[3][cp12]/46,XY[3]
13	61	M	CML	45~46,XY,t(1;3)(p36;q21)[cp7],del(2)(p12)[3],-7[6], i(15)(q10)[2] [cp7]
14	64	M	MDS	45~47,XY,del(1)(p35)[cp9]/45,X,-Y[4]/46,XY[7]

Table 1: Continue

Case	Age, years	Gender	Clinical diagnosis	Karyotype
15	70	M	DLBCL	39~44,XY,+1[2],del(1)(p32p36.1)[9],del(1)(p31)[3], t(1;9)(p31;p22)[2],-6[15],add(6)(p25)[15],add(7)(p22)[15], del(8)(q24.1)[15],del(9)(q22)[13], add(9)(p24)[11], add(10) (q26)[15],+11[15],-13[3],add(14)(q32)[15] -15[11],-16[6],add(16)(p13.3)[15],-17[15],-18[5], add(18)(p11.3)[10],-19[7], add(19)(p11)[6],-20[3], add(22)(p11.2)[cp15]
16	75	M	B-ALL	45~50,XY,+1[12],del(1)(p22)[12],t(5;8)(p13?;q13?)[12],+7[8], t(7;8)(q11?;q11?)[10],-8[12],-9[10],add(9)(p23?)[11],+12[11], t(12;13)(q12;q12)[12],-13[12],add(14)(q32)[12],add(18)(q21?)[8], +19[10],der(19)t(19;?)(p13?;?)[12],+mar1[11],+mar2[5][cp12] / 46,XY[24]
17	39	F	Follicular NHL	46~50,XX,+X[4],+1[3],del(1)(p21)[4],+3[3],+7[6],add(8)(q23)[3], -9[6],add(14)(q32)[4],+mar1[4],+mar2[3][cp6]
18	56	M	MDS	39~44,(XY),+1[15],del(1)(p11)[16],-5[17],-7[17],-12[17],-14[4], -15[9],-16[17],-17[3],-19[17],-20[6],-22[17],+mar1[17],+mar3[17], +mar4[5],+mar5[2],+mar6[14],+mar7[2],+mar8[3][cp17]

MDS: Myelodysplastic syndrome, AML: Acute myeloid leukemia, AML M2: acute myeloblastic leukemia with maturation, ALL: acute lymphocytic leukemia, B-ALL: B cell acute lymphocytic leukemia, CML: Chronic myeloid leukemia, MM; Multiple myeloma, ITP: Idiopathic thrombocytopenic purpura, DLBCL: Diffuse large B-cell lymphoma, NHL: Non-Hodgkin's lymphoma, AA: Aplastic anemia

Table 2: Distribution of chromosome 1p aberrations in our cases

1p abnormalities	MDS	AML	ALL	CML	MM	ITP	DLBCL	Follicular NHL	AA
del(1)(p32p36)							1		
del(1)(p35)	1								
del(1)(p22)			1						
del(1)(p21)								1	
del(1)(p11)	1								
add(1)(p36)		1		2	2				
add(1)(p34)		1							
t(1;3)(p36;p21)		1							
t(1;3)(p36;q21)				2					
t(1;10)(p36;q21)				1					
t(1;2)(p36;q11)	1								
inv(1)(p36q41)									1
der(1)t(1;1)(p36;q21)						1			
der(1) (1qter→1q12::1p36→1qter)				1					

MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, ALL: acute lymphocytic leukemia, CML: chronic myeloid leukemia, MM: multiple myeloma, ITP: idiopathic thrombocytopenic purpura, DLBCL: diffuse large B-cell lymphoma, NHL: Non-Hodgkin's lymphoma, AA: aplastic anemia

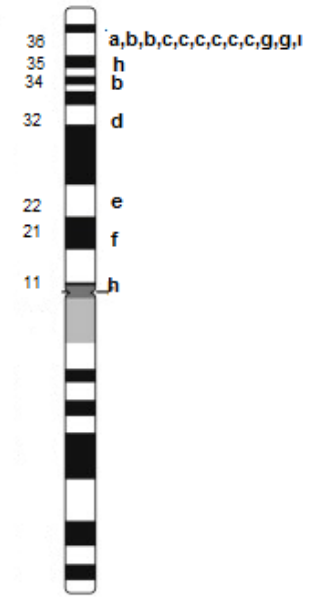

Figure 1: Distribution of hematologic malignancies by breakpoints in chromosome 1 ideogram
a: AA; b: AML, c: CML, d: DLBCL, e: ALL, f: Folicular NHL, g: MM, h: MDS, ı:ITP

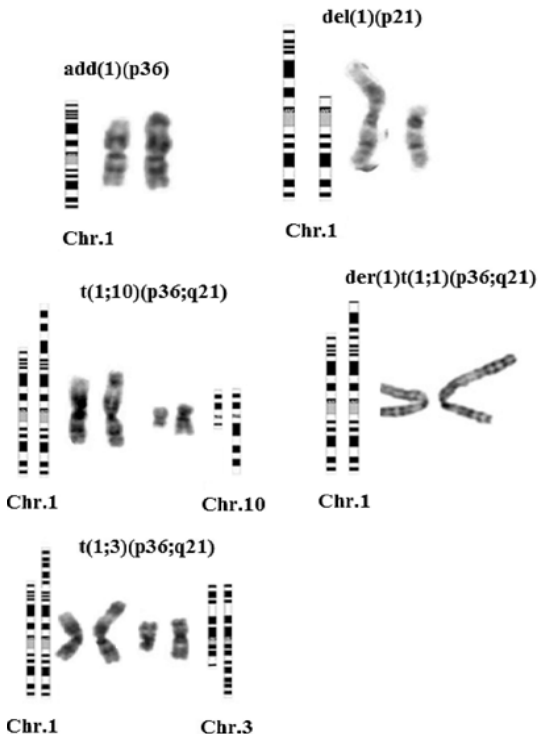

Figure 2: Examples of deletion and rearrangements at 1p36 with ideograms
Chr: Chromosome, add: Addition, del: Deletion, t: Translocation, der: Derivative

DISCUSSION

Structural aberrations of the short arm of chromosome 1 (from 1p11 to 1p36) involving balanced and unbalanced translocations, inversions, deletions, and duplications are very common in most hematologic malignancies. 1p contains numerous genes that are important in oncogenesis (4, 5, 9, 20, 21). *PRDM16* encodes a zinc-finger transcription factor, and this protein is known to induce the development of myeloid leukemia. It is an important predictive marker for poor prognosis in adult AML patients (6, 10, 20, 21). Deletion of the *CDC2L1* gene locus, which codes a protein kinase implicated in apoptotic signaling, has been observed in 88.5% of NHL cases containing 1p36 abnormalities (4). TNFRSF14 is a tumor necrosis factor receptor family member and a tumor suppressor whose loss promotes germinal center lymphomagenesis. *TNFRSF14* mutations tend to occur later in the pathogenesis of FL (7). Additionally, tumor suppressor genes such as DFFB, PRKCZ, MMP23B, ERRF11, and the SK1 proto-oncogene have been reported to be associated with different solid tumors localized to 1p36 (12-16).

The most commonly observed abnormality was add(1)(p36) in our series. We detected this addition in five patients (one AML, two CML, and two MM cases). The add(1)(p36) finding was also reported by Duhoux et al. as the most frequent abnormality in their hematologic malignancy series with 1p36 aberrations (22). Yoshida et al. also reported a case with add(1)(p36) in a complex karyotype of an AML case (2).

The other chromosomal addition in our study was add(1)(p34) in an AML patient. We could not find another case with this abnormality in our literature and database research (23).

Deletions that involve the 1p36 region are frequently seen in both myeloid and lymphoid neoplasms. We detected five patients with deletions at different breakpoints from 1p11 to 1p36, which were: del(1)(p11) and del(1)(p35) in MDS, del(1)(p21) in follicular non-Hodgkin's lymphoma, del(1)(p22) in ALL, and del(1)(p32p36) in DLBCL. Although there was no report for del(1)(p11) in our search of the literature, we found two reports of MDS cases with the 1p11 breakpoint in translocations with different chromosomes, namely der(1)t(1;16)(p11;p11.1) (24), and t(1;7)(p11;p11) (25). While not reported in the literature/database as del(1)(p35), we found a deletion of the region within an interstitial deletion as del(1)(p34p36) in an MDS case in our database research (23). We detected deletion of 1p21 in one patient with follicular non-Hodgkin's lymphoma. There are reports of the same deletion in follicular lymphoma patients (26, 27). We observed a del(1)(p22) in ALL, and Carbone et al. reported a FAB-L1 ALL case with del(1)(p22), too (28). We had a DLBCL case with an interstitial deletion of del(1)(p32p36). Belaud-Ro-

tureau et al. showed a terminal deletion at 1p36 in four of their large B cell lymphoma patients (29).

Patients with loss of heterozygosity (LOH) of 1p in MDS, AML, and MM are reported to have poor survival (4, 6, 30-32). Several researchers working on MDS reported that chromosome 1 abnormalities are often involved in the cytogenetic evolution of disease (33, 34). Frequent observations of 1p deletions in both hematologic malignancies and solid tumors suggest the presence of tumor suppressor genes encoded in this region. Most 1p deletions involve large regions; therefore, multiple tumor-suppressive genes might be lost in this setting (34-36). Various research groups have reported that deletion 1p correlates with tumor histopathology, tumor evolution, and disease progression (3, 37, 38). Because numerous genes with a potential role in malignant transformation are located at 1p22~1p36, detection of these deletions in chromosome analyses may indicate progression of the malignancy (30, 39-41). Süreyya et al. also reported in their case series that MM cases in which they detected deletions between the p21-p36 regions had short survival times (42).

We observed reciprocal translocation of 1p with other chromosomes in five patients as follows: t(1;3)(p36;q21) in 2 patients with CML, t(1;3)(p36;p21) in one patient with AML M2, t(1;2)(p36;q11) in one patient with MDS and, t(1;10)(p36;q21) in one patient with CML.

The t(1;3)(p36;q21) finding, which we observed in two CML patients, one of whom also had metastatic lung cancer, is a prominent finding in hematologic malignancies (9, 15, 43).

We detected t(1;3)(p36;p21) in one patient with AML M2. Sato et al. reported the finding of t(1;3)(p36;p21) in various hematologic malignancies such as MDS, AML, and CML. In the same way, we found t(1;3)(p36;p21) together with structural and numerical abnormalities of other chromosomes in our case. This patient was in the high-risk group based on the International Prognostic Scoring System (IPSS) and had a poor prognosis. Bai et al. also reported that they had AML patients with the same finding and poor prognosis (44).

We also observed t(1;2)(p36;q11) in one patient with MDS and t(1;10)(p36;q21) in one patient with CML. We could not find the exact match of these abnormalities in our literature search.

We identified derivative chromosomes in two cases. One of them was der(1)t(1;1)(p36;q21) in an ITP case and the other was der(1)(1qter→1q12::1p36→1qter) in a CML case, Duhoux et al. reported t(1;1)(p36;q12) as the most common anomaly in hematologic cancers (9). The inv(1)(p36q41) we detected in an AA case was the only inversion in our series, and we could not find the same inversion in the literature.

The distribution of breakpoints in different 1p abnormalities was remarkable in our study. In total, 12 out of 18 1p breakpoints were 1p36. However, while 1p breakpoints aggregated on 1p36 in all translocations, there was only one 1p36 breakpoint in five deletions, and it was one of the two breakpoints of the interstitial deletion.

It is also noteworthy that rearrangements involving 1p36 were observed mostly in CML cases in our series. Six out of 12 patients with 1p36 anomalies were CML, while others had different diagnoses.

The 1p36 breakpoint is well known as a hot spot for cancer-related chromosome rearrangements. There are different reports in the literature with rearrangements of 1p36 in different malignancies, and multiple genes in 1p36 are reported to have prognostic effects in various neoplasms. These genes are significantly associated with worse treatment response to targeted therapies and poor prognosis (4, 45-49). The PR/SET domain containing 16 (PRDM16), one of the genes that reside on 1p36, is fused with AF3p21 at 3p21 in t(1;3)(p36;p21), while with RPN1 (Ribophorin 1) at 3q21 in t(1;3)(p36;q21) in AML and MDS (43,50). It is reported that translocations of PRDM16 with RPN1 at 3q21 lead to its overexpression of PRDM16, and affected patients (AML, MDS, and CML) have a poor response to chemotherapy as well as poor prognosis (9). Sato Y et al. reported the finding of t(1;3)(p36;p21) in various hematologic malignancies such as MDS, AML, and CML. Also, they declared that the karyotypes in all cases were complex, and the t(1;3)(p36;p21) had been found together with structural and numerical abnormalities of other chromosomes. It has been observed that the prognosis of the patients varies from case to case (1).

Even in the new era of Next Generation Sequencing (NGS), cytogenetics, which is the only technique capable of detecting balanced chromosome abnormalities while observing the genome as a whole, remains the gold standard for the evaluation of hematologic malignancies. However, due to the technical difficulties of cancer cytogenetic studies and new developments in molecular techniques, the addition of new karyotype findings to the literature has been decreasing in recent years. Therefore, it is crucial to add cytogenetic results to the literature whenever possible, especially with complete karyotype formulas, which is the only way to access rare and previously unmentioned abnormalities (38).

CONCLUSION

In conclusion, we demonstrated rearrangements of 1p in 18 cases with hematologic malignancies by conventional cytogenetic methods and compared our results with

the literature. 1p rearrangements are seen as one of the main irregularities in myeloid and lymphoid hematologic malignancies. The frequency of these abnormalities in hematologic cancers implies the importance of this genomic region in carcinogenesis and disease progression. Survival data suggest that patients with myeloid malignancy and 1p rearrangements have a poor prognosis (9). Finally, these abnormalities can serve as biomarkers for prognosis when detected during routine cytogenetic follow-up of the patients. Therefore, the application of conventional cytogenetics during follow-up as well as at the time of diagnosis continues to be important in predicting the prognosis.

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