Jumping translocations of 1q in a child with t(2;8) acute lymphoblastic leukemia

Ten SK, Tan SK, Zubaidah Z and Khuzaiah RR[1] *Division of Haematology, Institute for Medical Research, 50588 Kuala Lumpur; [1]Pediatric Institute, Hospital Kuala Lumpur, 50586 Kuala Lumpur, Malaysia*

Abstract

Jumping translocation (JT) is an unusual type of chromosomal rearrangement whereby the same chromosome segment (donor) is translocated onto other chromosomes usually resulting in different unbalanced karyotypes. JT is rarely reported in hematological malignancies and may represent a poor prognostic factor. We report a case of a 4-year-old boy with acute lymphoblastic leukemia (ALL) - L3 subtype whose bone marrow cells had seven cytogenetically abnormal bur related subclones, with various unbalanced translocations resulting in trisomies for different segments of the long arm of chromosome 1. The only consistent abnormality present in all the subclones was t(2;8)(p12;q24), a translocation associated with ALL-L3. Our case is the first report of a JT involving 4 breakpoints on 1q in a t(2;8)-positive ALL with Yq as one of the recipient chromosomes.

Key words: jumping translocation; acute lymphoblastic leukemia; related subclones, t(2;8), 1q

Introduction

Mature B-cell acute lymphoblastic leukemia and Burkitt's lymphoma (BL) are often characterized cytogenetically by the presence of reciprocal translocation t(8;14)(q24;q32) and less frequently by variant translocations, t(2;8)(p12;q24) and t(8;22)(q24;q11). Patients with these translocations have a poor prognosis and may be referred to as a high-risk group (Gibbons & Czepulkowski, 1992).

Jumping translocation (JT) is an unusual type of chromosomal rearrangement whereby the same chromosome segment (donor) is translocated onto other chromosomes usually resulting in different unbalanced karyotypes.

In this paper, we report on the karyotypic evolution of a t(2;8)-positive ALL-L3 case showing "jumping" translocations involving different segments of the long arm of chromosome 1 (1q).

Materials and Methods

Case Report

MA was a 4-year-old Malay boy who was referred to the Paediatric Institute, Kuala Lumpur in February, 1994 for acute renal failure. He presented with fever, facial puffiness, abdominal pain and cervical swelling. On examination he was found to be pale, had slight bleeding from ulcers on upper and lower lips, and had hepatosplenomegaly and generalised lymphadenopathy in the axillary and inguinal region. Full blood count indicated a low hemoglobin level (8.4 g/dl), low platelet (53,000/cu mm) but raised white cell count (52,800/cu mm) with 90% blasts and low reticulocytes. The bone marrow was hypercellular with 91% blasts, predominantly of L3 morphology, which were negative for myelo-peroxidase and periodic acid-Schiff staining. Immunophenotyping confirmed a diagnosis of B-ALL (FAB-L3 type). Patient was started on B cell chemotherapy protocol but failed to respond and died 12 days after presentation from massive gastrointestinal bleeding.

Cytogenetic Studies

The patient's bone marrow sample was cultured in supplemented RPMI medium with 20% fetal calf serum and harvested using the direct technique and after 24-hour incubation. The chromosome slides were then banded using the standard trypsin-Giemsa banding technique. The analysis of the metaphases was done in accordance with the new guidelines for cancer cytogenetics (ISCN 1991). An *abnormal clone* is defined as two or more cells with the same extra or structural abnormality or as three or more cells lacking the same chromosome. A *subclone* is defined as one or more cells of a clone with chromosome abnormalities in addition to the primary abnormality of the clone. The *mainline* is the most frequent chromosome constitution of a tumor cell population. The *stemline (sl)* is the most basic clone of a tumor cell population or cells with the simplest karyotype.

Results

Seven abnormal but related subclones were detected. The primary karyotypic change was t(2;8)(p12;q24), thus the *stemline* was confirmed as *46, XY, t(2;8)(p12;q24)*. Jumping translocations of chromosome 1q were seen in 5 subclones. These resulted from 4 breakpoints (q21, q25, q32, q42) on chromosome 1q with subsequent transfer of the chromosome 1q segments to the telomeric regions of 3 different recipient chromosomes (4p, 13q, Yq). Five detivative chromosomes were formed, namely: *der(4)t(1;4)(q21;p14), der(4)t(1;4)(q32;p14), der(13)t(1;13)(q25;q34),*

der(13)t(1;13)(q42;q34) and *der(Y)t(Y;1)(q12;q21)*. The most frequently occurring subclone (or mainline) as seen in 30 spreads had the derivative chromosome 4, *er(4)t(1;4)(q21;p14)* in addition to r(2;8) translocation (Fig. 1). Partial karyotypes of the other derivative chromosomes are as shown in Fig. 2. Ten other metaphases showed an additional abnormality, *t(9;13)(q12;q34)* (Fig. 3).

Discussion

The cytogenetic findings described here are consistent with the clonal evolution of a t(2;8)-positive cell clone to a more complex karyotype which included the partial trisomies of chromosome 1q and a t(9;13) translocation. The presence of t(2;8) in the stemline of the patient's marrow supported the diagnosis of ALL-L3. It is now known that as a result of the (2;8)

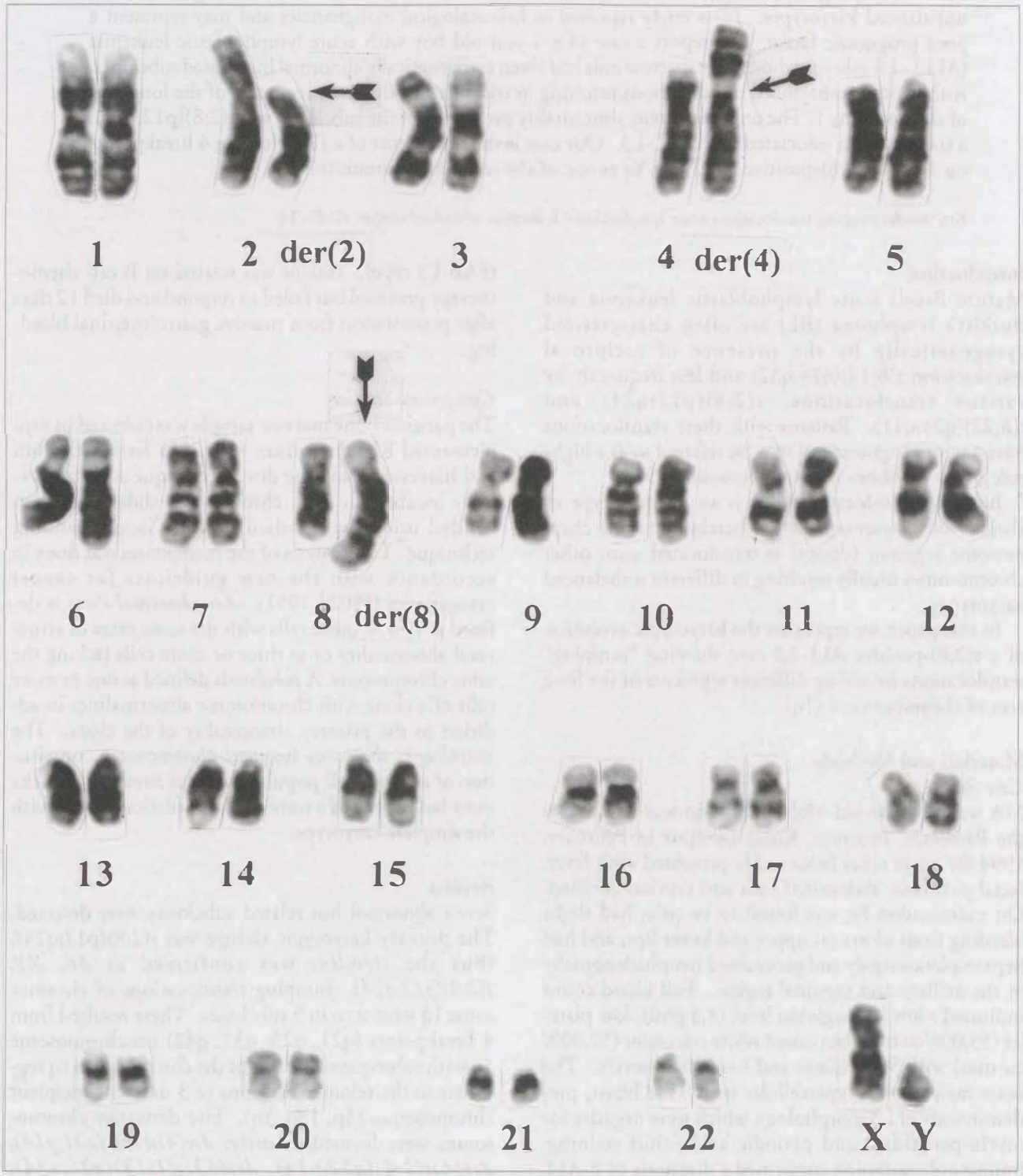

Fig. 1. Karyotype of mainline seen in 30 spreads: 46, XY, t(2;8)(p12;q24), der(4)t(1;4)(q21;p14).

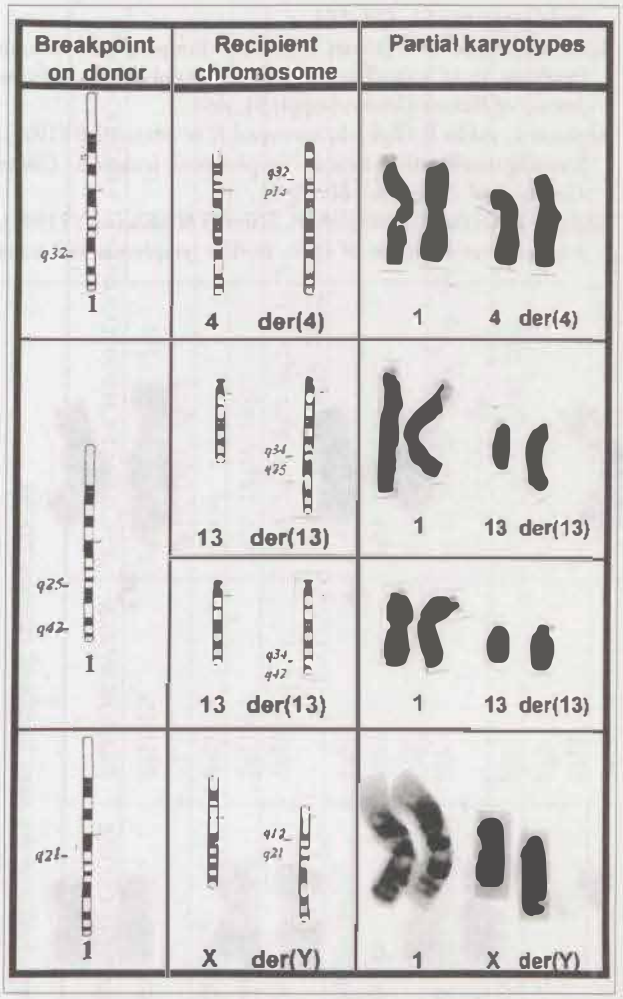

Fig. 2. Idiograms and partial karyotypes of jumping translocations with 4 breakpoints on 1q. (i) der(4)t(1;4)(q32;p14) [7] (ii) der(13)t(1;13)(q25;q34) [3] (iii) der(13)t(1;13)(q42;q34) [3] (iv) der(Y)t(Y;1)(q12;q21) [2].

translocation, the c-myc oncogene at 8q24 is juxtaposed next to the kappa light chain locus at 2p12, causing dysregulation of c-myc, increased transcription and, consequently, neoplastic growth.

JT is a rare phenomenon and to our knowledge only 20 such cases have been reported in hematological malignancies (Table 1). JT of chromosome 1q as the donor chromosome is most frequently reported and particularly in B-cell acute lymphoproliferative disorders. These JT were often present concomitantly with another chromosome translocation specific for the defined type of disease, such as t(8;14) in B-ALL/Burkitt's lymphoma (Morris *et al.*, 1984; Shikano *et al.*, 1993), t(4;11) in null ALL (Shippey *et al.*, 1990) and t(14;18) in follicular lymphoma (Wlodarska *et al.*, 1994). These findings suggest that JT are not specifically related to the genesis of these malignancies, but may rather confer a proliferative advantage to the malignant clone (Morris *et al.*, 1984; Wlodarska *et al.*,1994). There is also a preferential involvement of the telomeric regions of the recipient chromosomes in JT, prompting the postulation that these telomeric ends may play a role in stabilizing jumping translocations in dividing malignant cells (Najfeld *et al.*, 1995).

Our case is unusual in three aspects, namely, this is the first report of jumping translocations occurring in a case of t(2;8)-positive ALL-L3, 4 breakpoints on 1q are involved and the first case of chromosome Yq as a recipient chromosome.

In summary this case study illustrates the wealth of information that can be obtained from a cytogenetic investigation of a hematological disorder. The unique karyotypic patterns of our patient's bone marrow cells nor only confirmed the diagnosis of the disease but also revealed the chromosome instability of the leukemic cells, probably a consequence of disease progression. Our study complements the findings of earlier reports on the increased frequency of occurrence of jumping translocarions in Burkitt-like leukemia / lymphoma, with a preferential involvement of 1q in most cases reported. Further studies are needed to provide insights on the role of 1q in the occurrence of this rare event and its possible significance.

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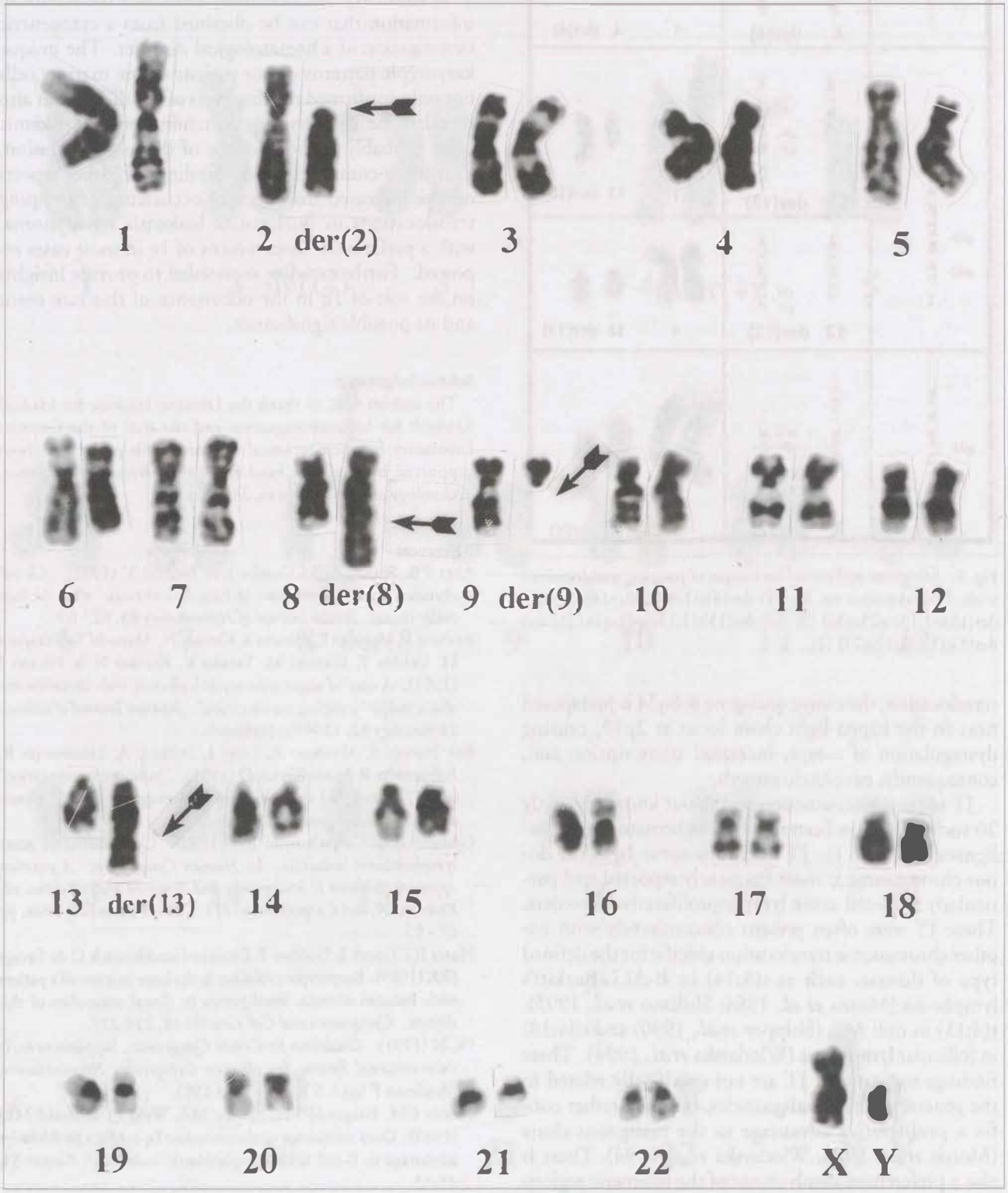

Fig. 3. Karyotype of sideline seen in 10 spreads: 46, XY, t(2;8)(p12;q24), t(9;13)(q12;q34).

Table 1. Diagnosis and breakpoints in 20 reported cases of hematological malignancies with jumping translocations

REFERENCES	DIAGNOSIS/FAB	SEX/AGE (YR)	ORIGINAL CLONE	DONOR BANDS	RECIPIENT CHROMOSOMES	# BREAKPOINTS
1. Morris *et al.* (1984)	B-ALL/L3	F/17	del(7), t(8;14)	1q11/12	7q36 11q25 13q3 15q2 18p11 21p1 Xp22	1
2. Whang-Peng *et al.* (1984)	BL-AIDS	M/23	t(8;14)	1q21	4q 19q	1
3. Raimondi *et al.* (1987)	L1	M/13	None	1q11/12	2q27 13q34 16q24	1
4. Shimohara & Nomura (1988)	L1	M/59	None	1q11/12	1q44 2q37 3q29 8q24 11q25 14q32 15q26 16q24 21q22 22q12	1
5. Huret *et al.* (1989)	FARA	M/21	del(5)(q21q23)	1q12	2q37 6p25	1
6. Shippey *et al.* (1990)	null ALL	M/68	t(4;11)	1q11 1q21	4q21 11q25 16q24 16q24 19p13	2
7. Shinohara *et al.* (1990)	L1	F/1	-9, 14p+, 15p+, -17, -22, +3 mar	NA	1q 2q 6q 7p 7q 9q 10p 12q 14p 17q 18p Xp	NA
8. Asahara *et al.* (1991)	M5b	M/37	NA	NA	i(1q) 12q 18q 19p 22q	NA
9. Ben-Neriah *et al.* (1991)	preBALL/AMMoL	M/17 mo	+22	1q2 1q11	20q 21p 14p	2
10. Reis *et al.* (1991)	M5a	M/74	+8, der(4)t(3;14)	3q13	1q 2p 4p 8p 8q 13p 14p 14q	1
11. Roland *et al.* (1992)	non-Burkitt's lymphoma	M/9 mo	t(8;14)	1q12	6q 14p 16q 19p 19q 21p	1
12. Alter *et al.* (1993)	FA	M/NA	None	1q21	18p11	1
13. Shikano *et al.* (1993)	BL	M/13	del(7), r(8;14)	1q21	1q 11p 13p 13q 14p 14q 17q 18p 18q Yp	1
	AML-M0	F/10 mo	+6,+8, +9, +19, +20	1q21	1p 5q 22p	1
	L3	M/6	t(8;14)	1q21	1q 13p 14p	1
14. Wlodarska *et al.* (1994)	Follicular lymphoma	M/46	t(14;18)	9q13	1p 13q	1
15. Naiffeld *et al.* (1995)	RAEB	F/56	+8	1q11	8p21 15p13 22p13	1
	MDS	M/NA	t(4;11), +11	1q11	21p13 22p13	1
	CML-BC	F/57	t(9;22)	7p11	1q42 22p11	1
16. Seghezzi *et al.* (1995)	L3	F/65	t(8;14)	1q11 1q21	14p 15p 22p 13q	2
17. Present study	L3	M/4	t(2;8)	1q21 1q25 1q32 1q42	4p14 Yq12 13q34 4p14 13q34	4

Abbreviations: FA, Fanconi anemia; RA, refractory anemia; AMMoL, acute myelomonocyric leukemia; AML, acute myeloid leukemia; RAEB, Refractory anemia with excess blast; MDS, myelodysplastic syndromes; CML-BC, chronic myeloid leukemia blast crisis; NA, not available

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