Atypical chronic myeloid leukemia with isochromosome (X)(p10): A case report

MASAHIDE YAMAMOTO, SAYAKA SUZUKI, JUN-ICHI MUKAE, KEISUKE TANAKA, KEN WATANABE, GAKU OSHIKAWA, TETSUYA FUKUDA, NAOMI MURAKAMI and OSAMU MIURA

Department of Hematology, Tokyo Medical and Dental University, Tokyo 113-8519, Japan

Received June 14, 2016; Accepted December 20, 2016

DOI: 10.3892/ol.2017.6595

Abstract. Atypical chronic myeloid leukemia (aCML) is a rare subtype of myelodysplastic/myeloproliferative neoplasm (MDS/MPN). Although recurrent chromosomal and genetic abnormalities are frequently observed in aCML, none are specific to this type of leukemia. The present study reported a case of aCML associated with i(X)(p10), a rare recurrent chromosomal abnormality of hematological malignancy. A 40-year-old female was referred to the Tokyo Medical and Dental University Hospital (Tokyo, Japan) due to slight leukocytosis and anemia. A bone marrow aspiration revealed 4% blasts and granulocytic hyperplasia with dysplasia. A G-banded cytogenetic analysis of the bone marrow cells revealed 46, X, isochromosome X(iX)(p10) in all metaphases. The percentage of the neutrophil precursors promyelocytes, myelocytes and metamyelocytes in the peripheral blood was >10% throughout the clinical course of the patient, which resulted in a diagnosis of atypical chronic myeloid leukemia. Treatment with hydroxycarbamide was not able to effectively alleviate leukocytosis, and the disease progressed with the appearance of an additional cytogenetic abnormality, t(10;17)(p13;q21). Subsequently, the patient underwent allogeneic stem cell transplantation from a sibling donor, and subsequent cytogenetic analysis revealed a normal karyotype with full donor chimerism. The isodicentric X(idicX)(q13) mutation is a similar abnormality to i(X)(p10) and may result in a loss of the X-inactive specific transcript gene located at Xq13.2, the deletion of which has been previously reported to result in the development of MDS/MPN in mice. In addition, i(X)(p10) was identified as the sole chromosomal abnormality at the diagnosis of aCML in the case of the present study, which is similar to patients from previous studies of other hematological malignancies and supports the hypothesis that i(X)(p10) may have served a primary role in the leukemogenesis of aCML.

Correspondence to: Dr Masahide Yamamoto, Department of Hematology, Tokyo Medical and Dental University, 1-5-45 Yushima, Tokyo 113-8519 Japan
E-mail: hide.hema@tmd.ac.jp

Key words: atypical chronic myeloid leukemia, i(X)(p10),t(10;17)(p13;q21), X-inactive specific transcript, idic(X)(q13)

Introduction

Atypical chronic myeloid leukemia (aCML) is a rare subtype of myelodysplastic/myeloproliferative neoplasm (MDS/MPN) with an incidence rate of 1-2 cases for every 100 patients with BCR-ABL1 positive CML (1). In the World Health Organization (WHO) 2008 classification, aCML is characterized as 'peripheral blood leukocytosis due to increased number of neutrophil and their precursors with prominent dysgranulopoiesis, with absent/minimal monocytosis or basophilia' (1). In ~40% of patients, aCML develops into acute myeloid leukemia with median survival times ranging between 12 and 29 months. An allogeneic hematopoietic stem cell transplantation (AlloSCT) is the only option to treat aCML, which is associated with poor prognoses (1,2).

Chromosomal abnormalities are exhibited by between 20 and 88% of patients with aCML, with +8, i(17q), or -7/-7q observed most commonly (2). Additionally, SET binding protein 1 (SETBP1) and ethanolamine kinase 1 (ETNK1) mutations are associated with aCML, according to previous studies (3,4). However, no specific recurrent chromosomal or genetic abnormalities have been identified in aCML thus far (5). Conversely, X chromosome abnormalities occur in ~1% of patients with hematological disorders, with i(X)(p10) considered a recurrent chromosomal abnormality in hematological malignancies (6).

In the present study, a case of adult aCML with i(X)(p10) and an additional cytogenetic abnormality appearing 1 year later was described. The cytogenetic abnormalities became undetectable subsequent to the patient undergoing AlloSCT.

Case report

A 40-year-old female was referred to the Tokyo Medical and Dental University Hospital (Tokyo, Japan), due to an annual medical checkup revealing slight leukocytosis and anemia, with a white blood cell count (WBC) of $12x10^9$/l (myelocyte, 2%; metamyelocyote, 6%) and a hemoglobin (Hb) level of 9.4 g/dl. A physical examination demonstrated no remarkable findings. A complete blood count exhibited the following results: WBC of $8.1x10^9$/l (differential: Blast 0%, promyelocyte

0%, myelocyte 0%, metamyelocyte 7%, neutrophil 56%, lymphocyte 19%, monocyte 18%), Hb level of 8.6 g/dl, a platelet count of $230x10^9$/l. The bone marrow morphology revealed 4% blasts, granulocyte proliferation with dysplasia and slight dysplasia in the megakaryocytic lineage identified by May-Giemsa staining with Giemsa and May-Grünwald solutions (Muto Pure Chemicals Co., Ltd., Tokyo, Japan), as presented in Fig. 1.

A G-banded cytogenetic analysis of the bone marrow cells revealed 46, X, i(X)(p10) in all metaphases analyzed, as illustrated in Fig. 2A, and subsequent chromosomal analysis of phytohemagglutinin-stimulated peripheral blood cells revealed the normal female karyotype 46, XX, as demonstrated in Fig. 2B. Fluorescent *in situ* hybridization (FISH) analysis did not detect the BCR/ABL fusion gene, and the results of the molecular genetic analyses were negative for the Janus kinase 2 (JAK2) V617F mutation, and mutations in granulocyte colony-stimulating factor receptor (CSF3R), SETBP1, and ETNK1.

The absolute monocyte count of the patient was $>1x10^9$/l, and the percentage of monocytes was <10%. Furthermore, the percentage of the neutrophil precursors promyelocytes, myelocytes and metamyelocytes was >10% throughout the clinical course of the patient. Based on these clinical and hematological findings, the diagnosis was aCML.

Initially, the patient did not receive any therapy, but exhibited a rapid increase in WBC to $43x10^9$/l in the 6 months following initial diagnosis, as demonstrated in Fig. 3. Subsequently, hydroxycarbamide therapy was initiated. However, the treatment did not induce an adequate hematological response. Furthermore, an additional cytogenetic abnormality, t(10;17)(p13;q21), was detected in 2/20 bone marrow cells analyzed 1 year following initial diagnosis. Therefore, the patient received AlloSCT from a human leukocyte antigen-matched sibling donor. Prior to this, the patient received 3.2 mg/kg/day intravenous busulfan, in 4 doses, between days 5 and 2 prior to AlloSCT treatment, 30 mg/m^2/day fludarabine between days 6 and 2 prior to AlloSCT treatment and total body irradiation using 400 cGy/day in 2 doses on the day of treatment initiation. Graft vs. host disease prophylaxis comprised a continuous infusion of cyclosporine A (2 mg/kg, from 1 day prior to AlloSCT treatment) and a short course of methotrexate (10 mg/m^2 on day 1 following AlloCST treatment, and 7 mg/m^2 on days 3 and 6 following AlloCST treatment). The patient was successfully engrafted with the donor cells on day 20 of transplantation. Post-transplant cytogenetic analysis revealed a normal male karyotype with full donor chimerism as measured by FISH analysis, showing the XY pattern in >99% of the bone marrow cells.

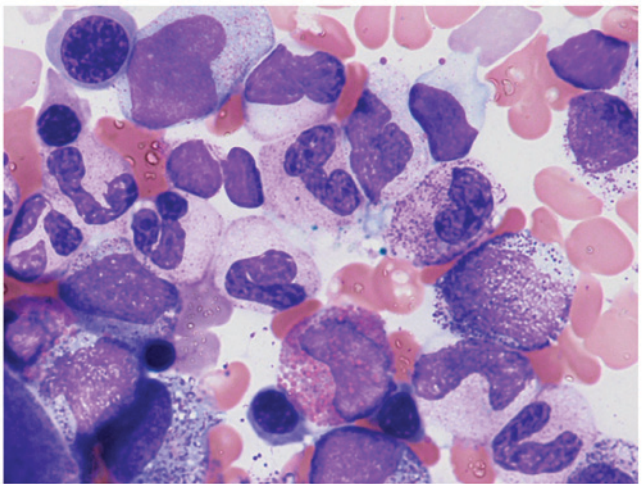

Figure 1. Bone marrow aspirate smear at point of diagnosis exhibiting hyperplasia of the granulocytic lineage with dysplastic changes. May-Giemsa staining; magnification, x400.

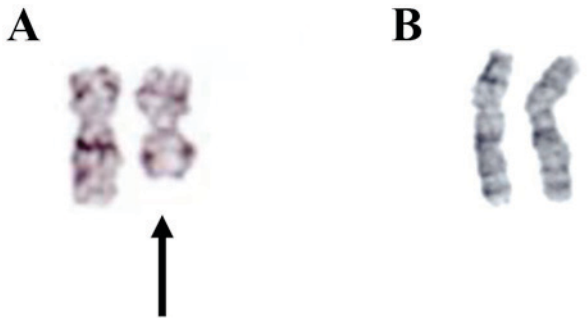

Figure 2. Partial G-banding karyogram demonstrating the X chromosomes of the bone marrow cells at (A) point of diagnosis and (B) in the phytohemagglutinin-stimulated peripheral blood cells. Arrow indicates i(X)(p10).

Discussion

Although recurrent chromosomal and genetic abnormalities are frequently observed, none are specific to aCML (7). Conversely, a number of genetic mutations have been reported with diverse frequencies: JAK2V617F at 4-8%; CSF3R at <10%; SETBP1 at 25% and ETNK1 at 8.8%. According to previous studies, mutations in SETBP1 or ETNK1 are strongly associated with aCML (3,4,7,8). In the present study, these mutations were not detected by the direct sequencing methods performed in previous studies. Therefore, the present case did not demonstrate the chromosomal abnormalities or genetic mutations previously reported in aCML (3,4,8).

X chromosome abnormalities occur in ~1% of patients with hematological disorders (6). At present, 26 cases with well-characterized i(X)(p10) have been reported, as demonstrated in Table I (6,9-12). All except one of the patients were female. Although the majority of patients exhibited myeloid malignancies, the present study is the first case of a patient with aCML exhibiting i(X)(p10) to be reported to date. It is notable that i(X)(p10) has been demonstrated to be the sole chromosomal abnormality or the abnormality in a stem line in ~50% of previously published studies (6), which suggests that it may serve an initial or primary role in leukemogenesis. However, detailed clinical courses of patients with i(X)(p10) have not been investigated to date. The patient of the present study exhibited i(X)(p10) as the sole chromosomal abnormality at the point of diagnosis of aCML, and acquired the additional t(10;17)(p13;q21) abnormality during the subsequent progression of the disease. This clinical course is compatible with the hypothesis that i(X)(p10) may serve a primary role in leukemogenesis. Furthermore, t(10;17)(p13;q21), which is rare recurrent chromosome abnormality in myeloid leukemia (13), is potentially associated with disease progressions such as the

Table I. Previously published cases of hematological malignancies with i(X)(p10).

Patient	Age	Gender	Disease	Karyotype	(Refs.)
1	74	F	AML	47,X,i(X)(p10),+i(X)(p10)/48,idem,+8/48,idem,+20	(18)
2	79	F	AML	47,X,i(X)(p10),+i(X)(p10)	(19)
3	76	F	MDS	46,X,i(X)(p10)	(20)
4	32	F	CML	47,XX,t(9;22)(q34;q11),+22,47,X,i(X)(p10), t(9;22),+22,48,X,i(X)(p10),+i(X)(p10),t(9;22),+22	(21)
5	26	F	HL	81-85,XX,-X,i(X)(p10),del(1)(p21),+i(2)(p10)x2, del(3)(q21),del(4)(q?25),i(4)(p10),i(4)(q10),+5,-6,-7,del(7)(q32), i(7)(q10),del(9)(q21q31),der(12)t (3;12)(q21;q22), -13,-13,-15,+16,del(17)(p11),-18,-18,-20,add(20)(q13), -22,-22,-22,i(22)(q10),+mar	(22)
6	75	F	CMML	46,X,i(X)(p10)/46,idem,del(20)(q11q13)	(23)
7	65	F	ALL	47,X,i(X)(p10),add(2)(p?),add(14)(q?),-19,+22,+r/47, idem,del(6)(q?),add(16) (q24)	(24)
8	33	M	ALL	46,X,+i(X)(p10),-Y/46,idem,del(17)(p12p13)/46,idem, del(7)(q32q36),del(17)	(25)
9	18	F	HL	59-83,XXX,-X,i(X)(p10),-1,+2,add(2)(q37)x3,+3,-6, del(7)(q12q22),-8,del(8) (q24),-9,-10,-11,-11,del(11)(q12q13), +12,-13,-13,-14,-15,-16,-17,-17,-18, add(20)(q13), +del(20)(q11q13),-21,+4mar	(26)
10	50	F	CML	46,X,i(X)(p10),t(9;22)(q34;q11),i(17) (q10)/50,idem,+1,+8,+13,+19	(27)
11	3	F	ALL	48,XX,+i(X)(p10),+21c	(28)
12	?	F	CMML	46,X,i(X)(p10)	(29)
13	74	F	AML	46, X, i(X)(p10) [5]/46, XX [7]	(30)
14	62	F	MDS	46,X,i(X)(p10)	(6)
15	62	F	AML	46,X,i(X)(p10)	
16	17	F	ALL	45,X,-X,r(20)/46,X,i(X)(p10),r(20)	
17	73	F	MDS	46,X,i(X)(p10),del(5)(q13q33)	
18	32	F	AML	47-50,XX,+i(X)(p10)x2,+8,+9	
19	49	F	MDS	46,X,i(X)(p10)	
20	76	F	MDS	46,X,i(X)(p10) or del(X)(q24)?c	
21	80	F	MDS	46,X,i(X)(p10)	
22	38	F	MDS	46,X,i(X)(p10)	
23	10	F	ALL	52, XX, i(X)(p10), +4, -7, ins(7;?)(q22;?), t(10;21)(q22;q22), +14, +der(15)t(9;15)(q12;p11.2), +21, +21, mar	(9)
24	68	F	t-AML	46, XX, del(20)(q11) [5]/45, X, i(X)(p10), -7, del(20)(q11) [20]	(10)
25	?	F	AML	46, XX, inv(3)(q21;q26) [1]/45, idem, -7 [11]/45, idem, i(X)(p10), -1 [8]	(11)
26	?	F	CMML	46, X, i(X)(p10)	(12)
27	40	F	aCML	46, XX, i(X)(p10)	Present case

F, female; M, male; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma: CMML, chronic myelomonocytic leukemia; ALL, acute lymphoblastic leukemia; t-AML, therapy-related AML; aCML, atypical CML.

additional cytogenetic abnormalities observed in BCR/ABL-1 positive CML.

Similar characteristics have been observed for patients exhibiting i(X)(p10) and idic(X)(q13), which is the most common X chromosome-related abnormality with ~30 cases reported (14). This abnormality occurs in females of advanced age (range, 55-87 years) with myeloid malignancies, including aCML, and is often observed as the sole abnormality (15). There are also similar structural abnormalities of the X chromosome in i(X)(p10) and idic(X)(q13) mutations, with the break points at the centromere and Xq13, respectively (6). Based on the clinical and cytogenetic similarities, it is hypothesized that the mutations may share a common mechanism for leukemogenesis. In this regard, previous studies have revealed that the gene dosage effect due to the simultaneous gain of Xp and loss of Xq may serve a crucial role for idic(X)(q13), which

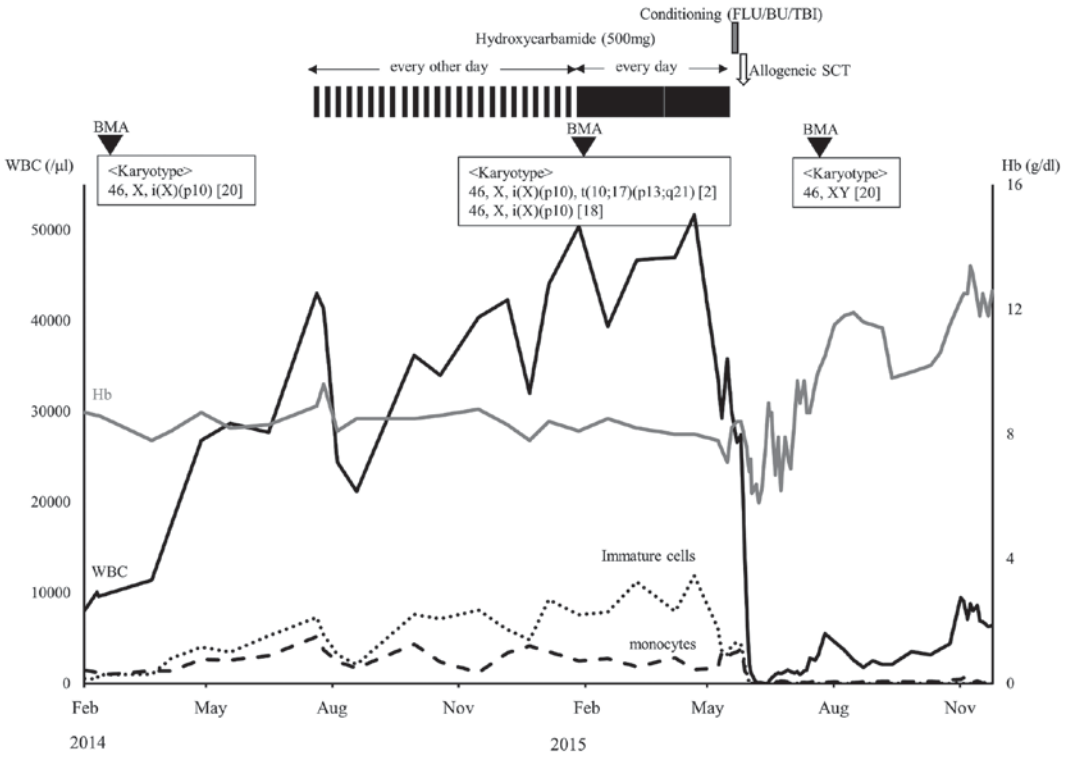

Figure 3. Clinical course of the patient. Solid black line, white blood cells; solid gray line, hemoglobin; dotted line, immature cells, promyelocytes, myelocytes and metamyelocytes; dashed line, monocytes; FLU, fludarabine; BU, busulfan; TBI, total body irradiation; SCT, stem cell transplantation; BMA, bone marrow aspiration.

does not result in formation of a fusion gene (6,14). Notably, the loss of Xq by idic(X)(q13) and i(X)(p10) results in the deletion of the X-inactive specific transcript (XIST) gene located at Xq13.2. XIST transcribes the long non-coding RNA XIST. The transcribed long non-coding RNA spreads along the X chromosome and serves an important role in the initiation of X inactivation in female cells. Additionally, there is considerable evidence that XIST RNA serves other important functions in the differentiation, proliferation and genome maintenance of human cells. Furthermore, loss of XIST RNA expression has been found in female breast, ovarian and cervical cancer cell lines, thus implicating the dysregulation of XIST in oncogenesis (16). Notably, a previous study demonstrated that the deletion of XIST in the hematopoietic cells in mice results in the development of MDS/MPN with 100% penetrance (17). Thus, a loss of XIST may serve a crucial role in the leukemogenesis of idic(X)(q13) or i(X)(p10) (6,14). Additional genetic and molecular analyses of i(X)(p10) and idic(X)(q13) in patients with MDS/MPN are required to establish the association of a loss of XIST with MDS/MPN in humans.

References

1. Vardiman JW, Bennett JM, Bain BJ, Brunning RD, Thiele J: Atypical chronic myeloid leukaemia, BCR-ABL1 negative. In: Swerdlow SH, Campo E, Lee Harris N, *et al* (eds): WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, pp80-81, 2008
2. Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, Chabot-Richards D, Weinzierl E, Hatem J, Jaso J, Kanagal-Shamanna R, *et al*: Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. Blood 123: 2645-2651, 2014.
3. Piazza R, Valletta S, Winkelmann N, Redaelli S, Spinelli R, Pirola A, Antolini L, Mologni L, Donadoni C, Papaemmanuil E, *et al*: Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. Nat Genet 45: 18-24, 2013.
4. Gambacorti-Passerini CB, Donadoni C, Parmiani A, Pirola A, Redaelli S, Signore G, Piazza V, Malcovati L, Fontana D, Spinelli R, *et al*: Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. Blood 125: 499-503, 2015.
5. Gotlib J, Maxson JE, George TI and Tyner JW: The new genetics of chronic neutrophilic leukemia and atypical CML: Implications for diagnosis and treatment. Blood 122: 1707-1711, 2013.
6. Adeyinka A, Smoley S, Fink S, Sanchez J, Van Dyke DL and Dewald G: Isochromosome (X)(p10) in hematologic disorders: FISH study of 14 new cases show three types of centromere signal patterns. Cancer Genet Cytogenet 179: 25-30, 2007.
7. Zoi K and Cross NC: Molecular pathogenesis of atypical CML, CMML and MDS/MPN-unclassifiable. Int J Hematol 101: 229-242, 2015.
8. Maxson JE, Gotlib J, Pollyea DA, Fleischman AG, Agarwal A, Eide CA, Bottomly D, Wilmot B, McWeeney SK, Tognon CE, *et al*: Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. N Engl J Med 368: 1781-1790, 2013.
9. Sharathkumar A, DeCamillo D, Bhambhani K, Cushing B, Thomas R, Mohamed AN, Ravindranath Y and Taub JW: Children with hyperdiploid but not triple trisomy (+4,+10,+17) acute lymphoblastic leukemia have an increased incidence of extramedullary relapse on current therapies: A single institution experience. Am J Hematol 83: 34-40, 2008.
10. Preiss BS, Bergmann OJ, Friis LS, Sørensen AG, Frederiksen M, Gadeberg OV, Mourits-Andersen T, Oestergaard B and Kerndrup GB; AML Study Group of Southern Denmark: Cytogenetic findings in adult secondary acute myeloid leukemia (AML): Frequency of favorable and adverse chromosomal aberrations do not differ from adult de novo AML. Cancer Genet Cytogenet 202: 108-122, 2010.
11. Lugthart S, Gröschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL, Jan Ossenkoppele G, Vellenga E, van den Berg-de Ruiter E, Schanz U, *et al*: Clinical, molecular, and prognostic significance of WHO type inv (3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol 28: 3890-3898, 2010.

12. Chen B, Ma Y, Xu X, Wang X, Qin W, Ji M and Lin G: Analyses on clinical characteristic and prognoses of 41 patients with chronic myelomonocytic leukemia in China. Leuk Res 34: 458-462, 2010.
13. Oh SH, Park TS, Cho SY, Kim MJ, Huh J, Kim B, Song SA, Lee JY, Jun KR, Shin JH, *et al*: Acute myeloid leukemia associated with t(10;17)(p13-15;q12-21) and phagocytic activity by leukemic blasts: A clinical study and review of the literature. Cancer Genet Cytogenet 202: 43-46, 2010.
14. Paulsson K, Haferlach C, Fonatsch C, Hagemeijer A, Andersen MK, Slovak ML and Johansson B; MDS Foundation: The idic(X)(q13) in myeloid malignancies: Breakpoint clustering in segmental duplications and association with TET2 mutations. Hum Mol Genet 19: 1507-1514, 2010.
15. Oscier DG: Atypical chronic myeloid leukaemia, a distinct clinical entity related to the myelodysplastic syndrome? Br J Haematol 92: 582-586, 1996.
16. Weakley SM, Wang H, Yao Q and Chen C: Expression and function of a large non-coding RNA gene XIST in human cancer. World J Surg 35: 1751-1756, 2011.
17. Yildirim E, Kirby JE, Brown DE, Mercier FE, Sadreyev RI, Scadden DT and Lee JT: Xist RNA is a potent suppressor of hematologic cancer in mice. Cell 152: 727-742, 2013.
18. Hagemeijer A, Hählen K and Abels J: Cytogenetic follow-up of patients with nonlymphocytic leukemia. II. Acute nonlymphocytic leukemia. Cancer Genet Cytogenet 3: 109-124, 1981.
19. Fitgerald PH, Morris CM, Fraser GJ, Giles LM, Hamer JW, Heaton DC and Beard ME: Nonrandom cytogenetic changes in New Zealand patients with acute myeloid leukemia. Cancer Genet Cytogenet 8: 51-66, 1983.
20. Knuutila S, Teerenhovi L and Borgström GH: Chromosome instability is associated with hypodiploid clones in myelodysplastic syndromes. Hereditas 101: 19-30, 1984.
21. Selleri L, Emilia G, Temperani P, Grassilli E, Zucchini P, Tagliafico E, Bonati A, Venezia L, Ferrari S, Torelli U, *et al*: Philadelphia-positive chronic myelogenous leukemia with typical bcr/abl molecular features and atypical, prolonged survival. Leukemia 3: 538-542, 1989.
22. Schlegelberger B, Weber-Matthiesen K, Himmler A, Bartels H, Sonnen R, Kuse R, Feller AC and Grote W: Cytogenetic findings and results of combined immunophenotyping and karyotyping in Hodgkin's disease. Leukemia 8: 72-80, 1994.
23. Nacheva E, Holloway T, Carter N, Grace C, White N and Green AR: Characterization of 20q deletions in patients with myeloproliferative disorders or myelodysplastic syndromes. Cancer Genet Cytogenet 80: 87-94, 1995.
24. Temperani P, Giacobbi F, Gandini G, Torelli U and Emilia G: Chromosome rearrangements at telomeric level in hematologic disorders. Cancer Genet Cytogenet 83: 121-126, 1995.
25. Martineau M, Clark R, Farrell DM, Hawkins JM, Moorman AV and Secker-Walker LM: Isochromosomes in acute lymphoblastic leukaemia: i(21q) is a significant finding. Genes Chromosomes Cancer 17: 21-30, 1996.
26. Falzetti D, Crescenzi B, Matteuci C, Falini B, Martelli MF, Van Den Berghe H and Mecucci C: Genomic instability and recurrent breakpoints are main cytogenetic findings in Hodgkin's disease. Haematologica 84: 298-305, 1999.
27. Barbouti A, Johansson B, Höglund M, Mauritzson N, Strömbeck B, Nilsson PG, Tanke HJ, Hagemeijer A, Mitelman F and Fioretos T: Multicolor COBRA-FISH analysis of chronic myeloid leukemia reveals novel cryptic balanced translocations during disease progression. Genes Chromosomes Cancer 35: 127-137, 2002.
28. Baker JM, Coppes MJ and Roland B: A case of Down syndrome with acute lymphoblastic leukemia and isochromosome Xp. Cancer Genet Cytogenet 147: 75-77, 2003.
29. MacGrogan D, Kalakonda N, Alvarez S, Scandura JM, Boccuni P, Johansson B and Nimer SD: Structural integrity and expression of the L3MBTL gene in normal and malignant hematopoietic cells. Genes Chromosomes Cancer 41: 203-213, 2004.
30. Bao L, Wang X, Ryder J, Ji M, Chen Y, Chen H, Sun H, Yang Y, Du X, Kerzic P, *et al*: Prospective study of 174 de novo acute myelogenous leukemias according to the WHO classification: Subtypes, cytogenetic features and FLT3 mutations. Eur J Haematol 77: 35-45, 2006.