American Journal of Clinical and Experimental Medicine
2014; 2(6): 128-131
Published online November 20, 2014 (http://www.sciencepublishinggroup.com/j/ajcem)
doi: 10.11648/j.ajcem.20140206.13
ISSN: 2330-8125 (Print); ISSN: 2330-8133 (Online)

Constitutional pericentric inversion of chromosome 9 and chronic myeloid leukemia

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To cite this article:
Salil Vaniawala, Gadhia Pankaj. Constitutional Pericentric Inversion of Chromosome 9 and Chronic Myeloid Leukemia. *American Journal of Clinical and Experimental Medicine.* Vol. 2, No. 6, 2014, pp. 128-131. doi: 10.11648/j.ajcem.20140206.13

Abstract: In the present study, we screened the bone marrow chromosome database entries between March, 2004 and December, 2013 to identify cases with inv(9) along with t(9;22) variations. Our study recorded 2300 cases of confirmed CML (Ph positive), of which only 12 (0.52%) cases had inv(9) and t(9;22). The association between inv(9) and t(9;22) is not fully explored. Therefore more number of cases is required to shed light on its important role, if any, especially in bone-marrow transplantation and drug resistance.

Keywords: Pericentric Inv (9), CML, t(9; 22), Bone-Marrow

1. Introduction

The frequency of constitutional chromosomal abnormalities in normal individuals has shown an increase because of improved banding techniques and modernization in karyotyping.. It has been well documented that inv(9) has been regarded as a normal variant (0.8 to 2.5%) in human population without phenotypic consequence. Few reports indicated that inv(9) has been associated with infertility and recurrent abortions[1-3], and various psychiatric disorders mainly schizophrenia[4]. It is highly speculative that whether or not constitutional inv(9) is predisposing factor(s) for cancers? However, evidences suggest that it might predispose to the development of laryngeal and ovarian cancers[5-6].

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease and characterized by the BCR and ABL somatic gene rearrangement. The constitutional inv(9) has been proposed as an advanced risk factor for patient with acute leukemia but association between inv(9) variation and CML or Acute lymphocytic leukemia (ALL) with Philadelphia (Ph) chromosome has been rarely documented. To our knowledge very few reports have been published on inv(9) and CML. Therefore, we studied retrospectively the incidences and clinical significance of inv(9) in large number of patients whose bone marrow was received at our laboratory for diagnostic purpose.

2. Materials and Methods

We retrospectively reviewed the bone marrow chromosome database at S.N.Gene Lab, and Research Centre, Surat, India between March, 2004 and December, 2013 in 2300 patients with suspected hematological diseases. Cytogenetic reports were reviewed and compared with available clinical data. Repeat results were not included. Informed concerned was taken from patients.

A standard culture technique for BM cells was employed and chromosomes were analysed using G- banding technique[7]. The cases with inv(9) and CML were identified and karyotyped described according to Int. System for Human Cytogenetics Nomenclature(ISCN)[8].

Fluorescence In Situ Hybridization (FISH) analysis was performed using freshly dropped slides from harvested bone marrow. The analysis was performed to confirm the presence of Ph translocation. Analysis of *BCR-ABL was* performed using commercial available *BCR-ABL* dual colour fusion probes (Abbot/Vysis, USA). A minimum of 200 interphase cells were scored.

3. Results

Our retrospective database searched revealed a total of 2300 adult cases of Ph- positive CML which was confirmed

by G-banded karyotyping and FISH techniques.

Of these 12 cases (0.52 %) were identified to have inv(9) along with CML. The data analyses reveal out of 12 patients 07 were females and 05 were males (Table – 1). The ages ranges from 21 years to 60 years old with mean age of 35 years.

In the present study cases nos. 1,3,5,7,9 and 10 which were earlier clinically diagnosed as CML, cytogenetic study of bone-marrow revealed karyotype either as 46,, XX, inv(9) (p11; q13), t (9; 22) (q34; q11.2) or 46, X Y, inv(9), (p11q13), t(9;22)(q34;q11.2). (Fig. -1).

Table 1. *Reported cases of inv(9) and t(9;22) variation in Ph-positive leukemia patients*

Case Number	Sex/Age	Diagnosis	Karyotypes
1	F/45	CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
2	F/28	BP-CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
3	M/25	CML	46XY,inv(9)(p11q13),t(9;22)(q34q11.2)
4	M/32	CP-CML	46XY,inv(9)(p11q13),t(9;22)(q34q11.2)
5	F/60	CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
6	F/25	BP-CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
7	F/25	CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
8	M/35	BP-CML	46XY,inv(9)(p11q13),t(9;22)(q34q11.2)
9	F/32	CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
10	M/21	CML	46XY,inv(9)(p11q13),t(9;22)(q34q11.2)
11	F/40	CP- CML	46,XX,inv(9)(p11q13),t(9;22)(q34q11.2)
12	M/56	BP-CML	46XY,inv(9)(p11q13),t(9;22)(q34q11.2)

CML – Chronic myeloid leukemia
BP-CML – Chronic myeloid leukemia - blastic phase
CP-CML - Chronic myeloid leukemia – chronic phase

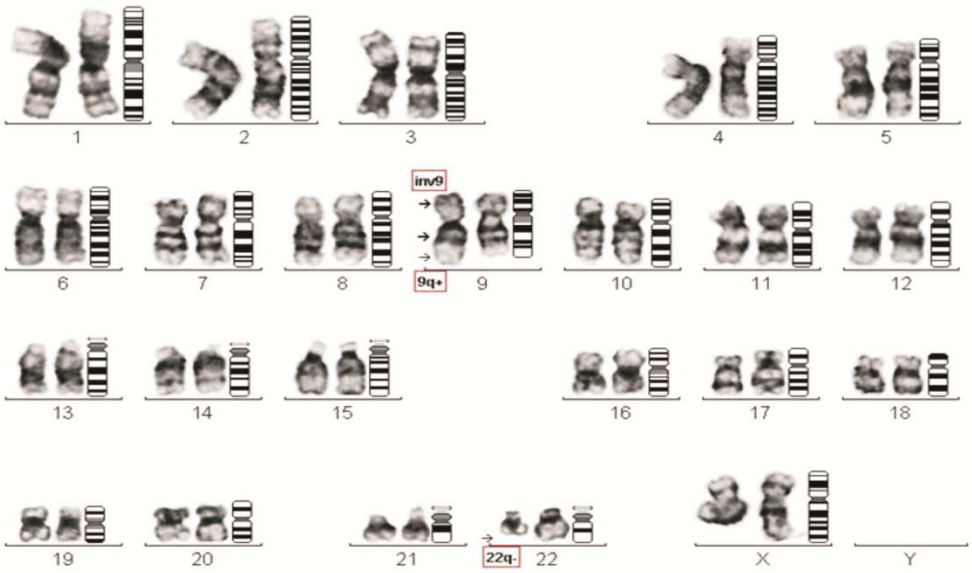

Fig. 1. *G-banded karyotype of patient no. 1 shows chromosome complement of 46XX,inv(9) (p11; q13), t(9;22) (q34; q11.2).*

On the other hand, cases nos. 2,6,8 and 12 clinically diagnosed as CML with blastic phase (CML-BP), where bone marrow examinations reported 60 to 90% blast cells (Table-1). The karyotyped showed either 46, XX, inv(9) (p11 q13), t(9; 22) (q34; q11.2) or 46, XY, inv(9) (p11 q13), t (9; 22) (q34;q11.2).

However, in case of Nos. 4 and 11 clinically diagnosed as CML-CP, cytogenetic study showed 46,XY,inv(9)(p11p13), t(9; 22)(q34 q11.2) or 46, XX, inv(9) (P11; q13), t(9; 22) (q34; q11.2) (Fig. – 2).

It is interesting to note here that in cases nos. 1,2,3,5,10,11 and 12 showed involvement of same chromosome # 9 both in CML translocation and inversion. While cases nos. 4,6,7,8 and 9 where two different chromosome #9 involved one in CML translocation and another one in inversion.

4. Discussion

In recent years the incidence of constitutional chromosomal abnormalities in apparently normal individuals

has increased. Pericentric inversion (9) is a common chromosomal aberration that may be involve in the mutagenesis of several types of cancer.

It is well known that constitutional inv(9) is a random chromosomal event that can be detected in any person. Inversion of chromosome 9 is not considered an important finding, reporting or publication bias may be responsible for few reports of inv(9) in the variaous hematological disorders [9].

It is difficult to predict that constitutional inv(9) is predisposing factor for hematological disorders. For instance, few reports indicated an excess of inv(9) in patients with Acute leukemia [10,11], but others failed to show similar results[12-13].

In the present study we found 12 cases of concomitant inv(9) and t(9;22) from 2300 cases of confirmed CML. Similarly, Suh et al.,[14] have carried out investigation with inv(9) and t(9;22) and found 4 cases of CML with inv(9).

It is established that CML patients showed good improvement with new tyrosine kinase inhibitors, but still few patients manifested resistance to drugs. The resistance cases of CML pertaining to constitutional or acquired inv(9) require to check thoroughly to understand the mechanism of resistance in CML patients in the presence of inv(9), if any.

It is concluded from the present study that though constitutional inv(9) is truly random chromosomal aberration, but its role in different cancers in general and CML in particular is needed to be investigated..

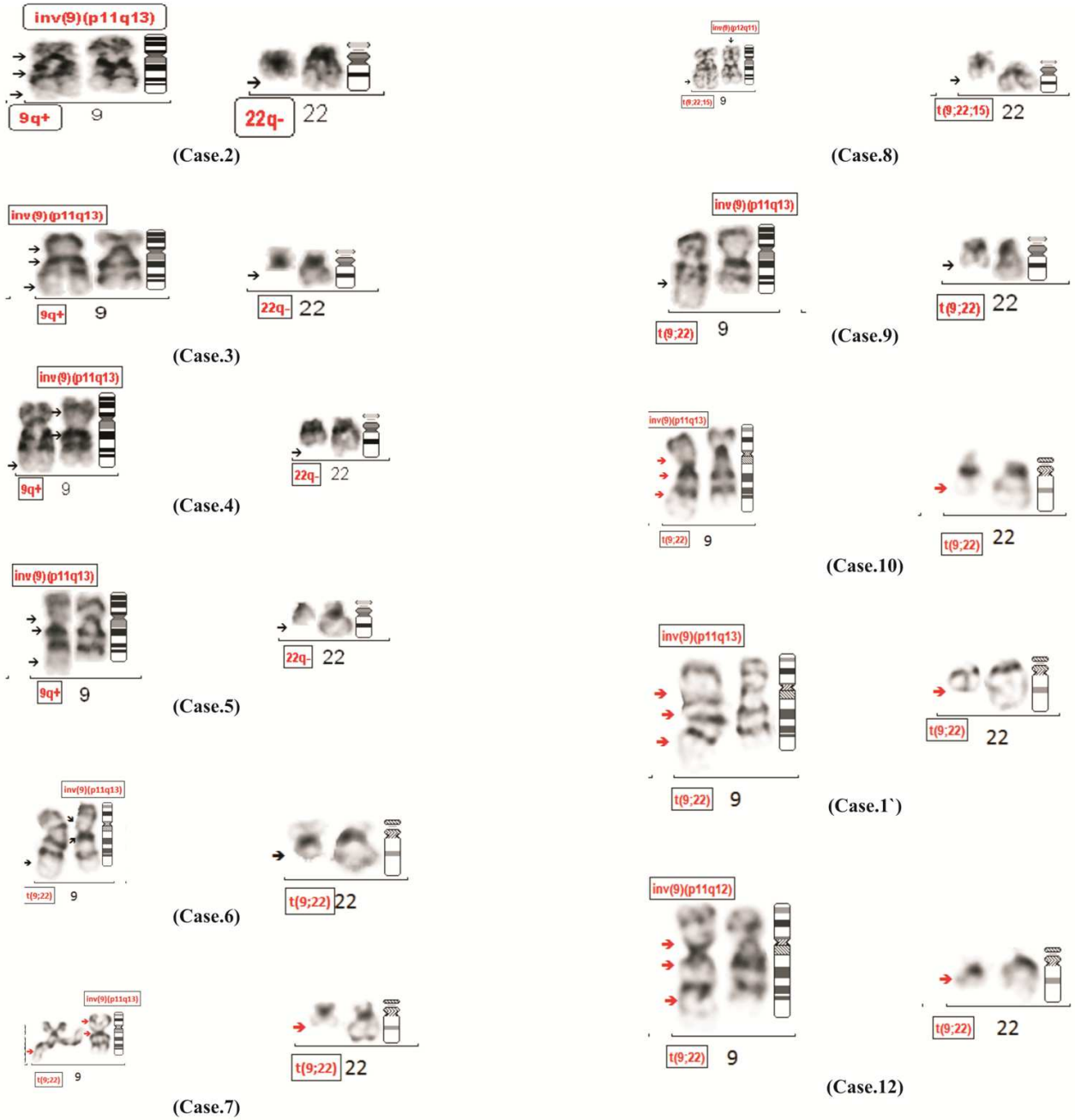

Fig. 2. *Partial karyotype showing inv(9) and t(9; 22) (q34; q11.2) found case nos. 2 to 12*

Acknowledgements

Authors wish to thank all technical assistants for their help and Mr. Urvish Dalal for arranging photographs in the manuscript.

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