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Rare Chromosome Structural Aberration Characterizing Oncology Malignancy

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Abstract

Ring chromosome aberration are rare abnormality potentially involving any chromosome in patients diagnosing in Oncology. The present review and case study has focused on the ring chromosome associated with oncology malignancies.

Material and Methods

An electronic peer review article search was performed systematically to obtain relevant literature with the CINAHL, Google scholar, and Pub Med databases. The keywords included marker, abnormalities, structural, Ring chromosome. The inclusion criteria for the review were that the documents were original quantitative research and published in English. This was also initiated using Medline, Mitelman database (<http://cgap.nci.nih.gov/Chromosomes/Mitelman>), Danish cytogenetic register and other pertinent web references on ring chromosomes in Oncology malignancies. Articles that were not directly relevant to the present objective were excluded. Also the un–stimulated bone marrow specimen of present

case manipulated with Methotrexate cells culture synchronization and finally was treated by GTG–banding technique.

Results

Ring chromosome was observed in 10% of the total cells. Cytogenetic analysis demonstrated apparently ring (15) 46, XY, r(15) karyotype. The clinical findings revealed history of nausea, loss of appetite, diarrhea, night sweats, and a weight loss, anemia and diagnosed as accelerated CML.

Conclusion

Our finding adds to the spectrum of both morphology and genetic rearrangements in oncology malignancies. Additional future analyses in similar subject will be necessary to draw firm conclusions.

Keywords

Ring chromosome; Marker; Malignancy; Mechanisms; Abnormality

Introduction

Ring chromosome aberration are rare abnormalities potentially involving any chromosome and the vast majority of previously reported cases were seen in patients with oncology malignancies. On the other hand, only few subjects carrying ring chromosomes with normal phenotype have been described⁽¹⁾.

Ring chromosome occurs in about 1/30,000 to 1/60,000 live births⁽²⁾. It is controversial that unstable (sub) telomere regions induce ring formation to

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consolidate the chromosome. During this fusion deletions, inversions, mutations and duplications can arise ^(2,3), resulting in a variable formation of ring chromosome in malignant disorder ⁽²⁾ and primary growth failure ⁽⁴⁾. Since all of the ring chromosome syndromes manifest with clinical abnormalities, it is assumed that the forming of the ring itself, irrespective of the involved genes, can generate clinical consequences ⁽²⁾. Ring formation has been reported for all type of human chromosomes ⁽⁵⁾.

Most of the ring chromosomes were embedded in highly complex karyotypes. This suggests that the ring chromosomes were secondary changes in the course of disease progression ⁽⁶⁾. There was no detailed, confirmatory report on an association between a certain leukemia subtype and a specific ring chromosome. The review summarizes a great number of reports on a total of 760 ring chromosomes in human neoplasias at different sites, but includes only cases with clearly identified rings ⁽⁷⁾. More commonly, they may arise as acquired genetic abnormalities in cells from tumors or leukemias. During tumor progression, the ring chromosomes can be broken and subsequently resealed ⁽⁸⁾. However, the mechanism underlying this process has not yet been sufficiently explained ⁽⁹⁾.

Mechanisms of ring formation

Ring chromosomes at cell division

In contrast to linear chromosomes, rings may undergo cell division in three different ways ^(10, 11). Which of these pathways a ring chromosome will follow depends on the number of sister chromatid exchanges (SCE) that has occurred in the ring before cell division:

1. No SCE or an even number of SCEs in the same direction will enable normal, symmetrical segregation of the chromatids.
2. An even number of SCEs in different directions will lead to the formation of interlocked rings.
3. An odd number of SCEs will lead to transformation from two parallel chromatids into one continuous ring, similar to a Mobius band with the double size of the original rings (Figure 1).

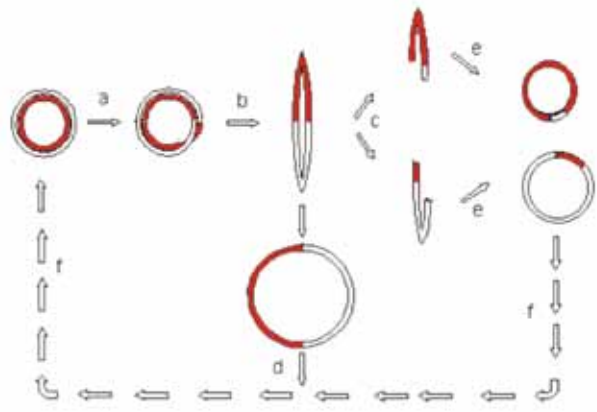


Figure 1 : Breakage–fusion–bridge cycle triggered by a sister chromatid exchange (a) leading to bridge formation (b) and breakage (c), or nondisjunction (d) at anaphase. Broken ends fuse in the daughter cells (e) and form novel ring structures, which can again undergo the same series of events (f).

Ring chromosomes may be formed in two ways as shown in Figure 2.

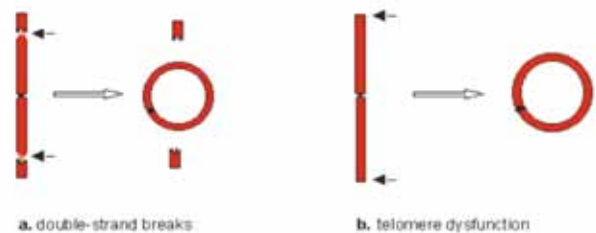


Figure 2 : Ring chromosome formation may occur through breaks in the chromosome arms and fusion of the proximal broken ends, leading to loss of distal material (a). Rings may also be formed by telomere dysfunction triggering fusion of reactive chromosome ends without major loss of genetic material (b).

1. By two DNA breaks, one in each arm of the same chromosome, followed by fusion of the proximal broken ends. The causes of these DNA breaks are usually unknown and so is the mechanism behind ligation of the ends. It is possible that the non-homologous end-joining machinery plays a role in this process ⁽¹²⁾. A ring can also be formed by fusion at two breakpoints in the same chromosome arm. However, only few examples of such rings have been described. Most probably, this is because they are acentric and will lack attachment point for the cell division machinery. Unless there is a different anchorage sequence for the kinetochore complex they will be lost in subsequent mitoses. Such “neocentromere” sequences have, however,

been described in rare cases of constitutional ⁽¹³⁾ and acquired ⁽¹⁴⁾ ring chromosomes.

2. By fusion of dysfunctional telomeres from the same chromosome. Several in vitro and animal models have shown that shortening of telomeric DNA repeats leads to the detachment of protective proteins from the chromosome ends ⁽¹⁵⁾. This renders the chromosome ends prone to recombination with DNA either from other chromosomes leading to formation of a dicentric or with the other arm of the same chromosome leading to formation of a ring.

Constitutional ring chromosomes

Constitutional ring chromosomes occur in 1/50,000 human fetuses ⁽²⁾. In most instances, these rings are formed by breakpoints in both arms, followed by fusion of the proximal ends into a ring with loss of the distal material. Such rings may thus result in clinical features mimicking terminal deletion syndromes. Alternatively, congenital ring chromosomes are supernumerary, i.e. they occur together with two normal homologues of the corresponding chromosome ⁽¹⁶⁾, and the consequences will be similar to partial trisomies or duplications. The ring syndromes are thus a very heterogeneous group, with different characteristics depending not only on which chromosome it is involved, but also on the position of breakpoints within the chromosome.

It should be noted however that ring syndrome patients do not only display diverse symptoms resulting from deletions or duplications. Most of them have one feature in common. In a meta-study including more than two-hundred patients with congenital ring chromosomes, it has been demonstrated that the majority of children with rings show a failure to thrive beyond the extent expected from their chromosomal imbalances ⁽¹⁷⁾. It has been suggested that this is due to the mitotic instability of rings, preventing somatic cells to proliferate normally. The hypothesis is supported by the fact that growth failure is more common among patients with large ring chromosomes, than among those with small ones ⁽¹⁷⁾. This is in accordance with the BFB model of ring chromosome dynamics. Statistically, large rings will undergo more SCEs per cell cycle than small rings and would thus have a higher propensity for breaking at anaphase. In a normal cell, this provokes a physiological DNA damage response leading to

either cell cycle arrest or apoptosis ⁽¹⁸⁾.

From the reasoning above, it follows that a cell population carrying a ring chromosome would proliferate slower than a population without rings; the population with rings would be less fit and be at a selective disadvantage. Interestingly, ring chromosome loss or size reduction is not uncommon in cases with congenital rings. In particular, cases with small rings often exhibit a subclone without the ring chromosome and these patients are thus ring/monosomy mosaics ⁽¹⁴⁾. In cases with large rings and prominent growth failure, heterogeneity of ring size is a more common feature. Children with ring chromosomes are thus illustrative examples of how natural selection at the cellular level may play a role for the symptoms and signs of human disease.

Acquired ring chromosomes

Hematological neoplasms		Carcinomas	
	%		%
Acute lymphoblastic leukemia	0.7	Breast	5.7
Chronic lymphocytic leukemia	1.1	Colon & rectum	4.6
Acute myelogenous leukemia	2.2	Gallbladder	21.1
Chronic myelogenous leukemia	1.0	Kidney	13.0
		Larynx	5.2
		Liver	13.0
		Lung	8.8
		Mouth	1.9
		Ovary	3.9
		Pancreas	11.5
		Prostate	0.0
		Skin	3.7
		Stomach	1.7
		Thyroid	1.1
		Uterine cervix	0.0
		Urinary bladder	4.5
		Uterus	2.2

Sarcomas	
	%
Chondrosarcoma	5.6
Dermatofibrosarcoma protuberans	70.3
Ewing sarcoma	0.6
Leiomyosarcoma	11.2

Table 1 : Ring chromosome prevalence (%) in human tumors*

*Data from the Mitelman Database of Chromosome Aberrations in Cancer, October 4, 2001. <http://cgap.nci.nih.gov/Chromosomes/Mitelman>

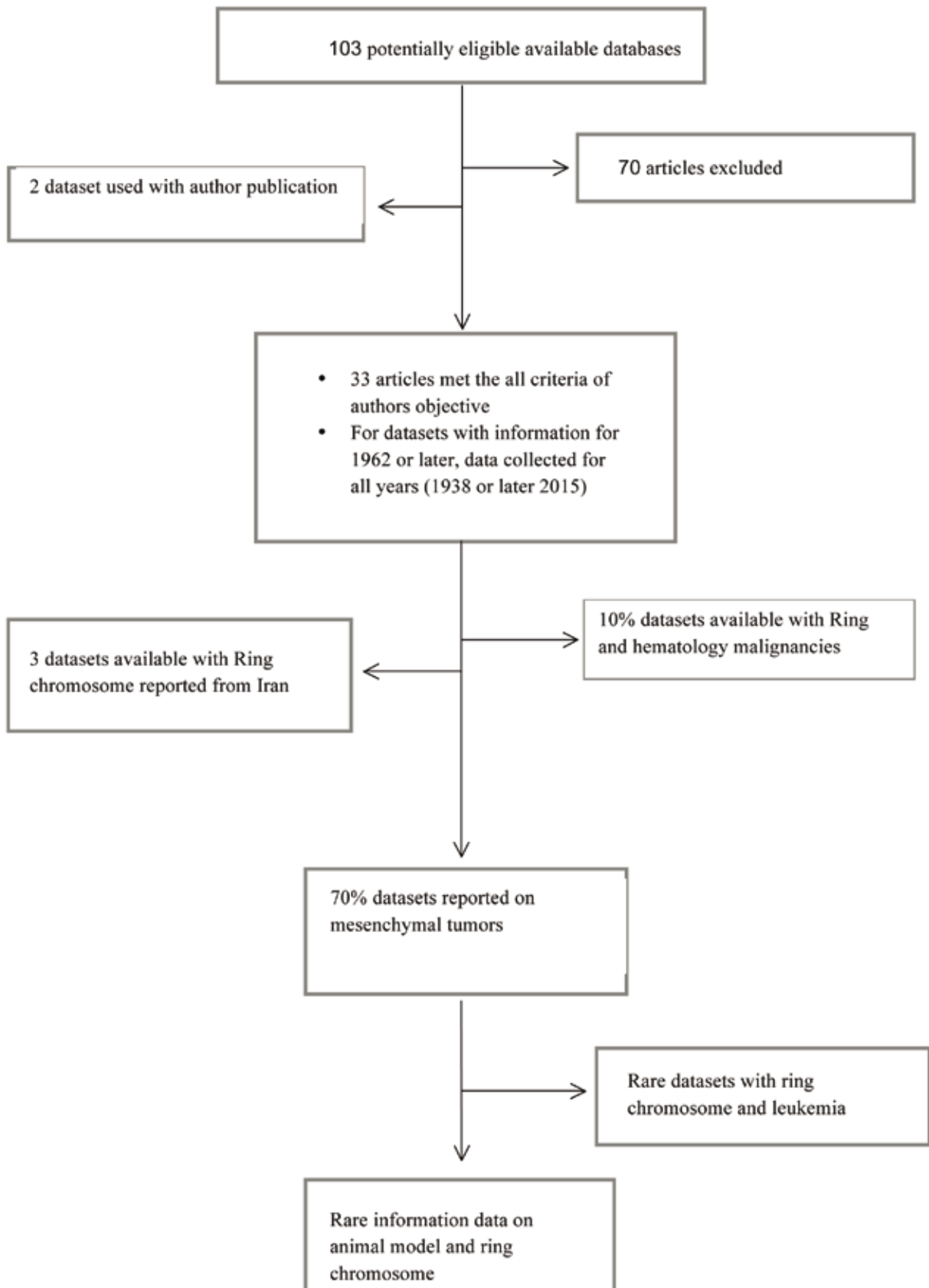


Figure 3 : Database selection process

Materials and Methods

The inclusion criteria for this review were that the documents were original, systemic review possessing qualitative and quantitative research, and published in English from January 1962 through May 2015 to assess existing knowledge on relationship between Ring chromosome and patients with Oncology malignancies. In the search process for the literature the authors retrieved documents that contained malignancy. Structural and numerical abnormalities, ring chromosome, heterogeneous population, cancer sites for cancer registration, and the most scientific databases were searched. English abstract, and full text of ProQues, MEDLINE/PubMed, CINAHL, (MeSH terms), Mitelman database (<http://cgap.nci.nih.gov/Chromosomes/Mitelman>), The Danish cytogenetic register, which contains data from all cytogenetic testing in Denmark from 1960 onwards (altogether 345,000 cases), were included. Articles that were not directly relevant to our specific objective questions were excluded. The software program as End Note was used to handle the proper references for instruction to author.

Chromosome preparations and banding Culturing, harvesting, and chromosome banding were essentially as previously described. Karyotypic descriptions were done according to ISCN (1995)⁽¹⁹⁾. At least 25 metaphase cells from parallel cultures were analyzed by G-banding.

Results

From the database, 103 articles were identified and after exclusion of duplicates, of which 33 articles were original, systemic review with qualitative and quantitative research, and published in English met the criteria for inclusion in the present review and case study article. Here, the major findings are summarized and presented under the following headings (Figure 3).

Cytogenetic features

During the last twelve years, chromosome banding studies were performed on 187 unselected consecutive either adults sex patients of de novo CML and AML at initial diagnosis^(20,21) in whom one interesting case of CML patient exhibited ring chromosome and was the subject of present

investigation. All patients were admitted to the major referral hospitals affiliated with Shahid Beheshti University of Medical Sciences, Tehran and other private clinics. The diagnosis of leukemia patients was based on characterization of the leukemic cells, obtained from bone marrow and/or peripheral blood, by cytochemical staining, immunophenotyping, cytogenetic and molecular cytogenetic when appropriate. Briefly, short term lymphocyte with 0.1–0.4 ml on bone marrow/peripheral blood was obtained using methotrexate call synchronization method⁽²²⁾ with minor modification. Cell culture were prepared using RPMI (Gibco Grand Island, NY, USA), which was supplemented with 20% fetal calf serum, antibiotics, and Phytohemagglutinin (Murex, Biotech Ltd, Darford, England). Two different cultures of each sample were prepared. The cells were harvested at 48h and 72h following stimulation, colchicines 0.004% (Sigma, chemical Co, St, Lois, Mo, USA) was added 1h prior to harvest. The cultures were centrifuged and subjected to hypotonic shock (20 min, 0.075M KCL) at 37°C. The lymphocytes were then fixed in acetic–methanol (1:3) and air dried with 5% aqueous Giemsa solution for 10 min. For each individual, 20 metaphases were analyzed for the presence of numerical and structural aberrations. Karyotypes were described according to International System for Chromosomes Nomenclature (ISCN)⁽¹⁹⁾.

Case presentation

A 53-year old male presented with a one month history of nausea, loss of appetite, diarrhea, night sweats, and a twelve pound weight loss. He had no significant past medical history and, despite his work in construction, denied any previous chemical or radiation exposure. Peripheral blood revealed anemia (Hb 8.2 g/dL), white cell count of 2.6×10^3 /uL. A bone marrow biopsy demonstrated a markedly hypercellular marrow (90–100% cellularity) with increased mature and immature granulocytes. The bone marrow aspirate contained myeloblasts. Cytogenetic analysis demonstrated apparently ring (15) 46, XY, r(15) karyotype (Figures 4, 5) in 19 of 34 evaluated metaphase cells and diagnosed as accelerated CML. Acquired rings are often difficult to characterize by chromosome banding techniques owing to the complexity of rearrangements, suboptimal banding quality, and shortage of material.

The cytogenetic delineation of ring chromosomes is further complicated by their structural instability.

Discussion

Because ring chromosomes are an uncommon cytogenetic finding and since there is a wide range in genetic abnormalities, exact and recent data about the relative frequency of ring formation for each chromosome are lacking.

There are only two cases with ring chromosome 18 with different address reported from Iran ^(23, 24). The present case might be the third one with different ring chromosome reported from here to accumulate the data for further investigation.

After the first report of a ring chromosome in a case of human leukemia by Sandberg et al., 1962 ⁽²⁵⁾, ring chromosomes have been infrequently (less than 10%) detected in hematopoietic neoplasias ⁽²⁶⁾. Whereas constitutional ring chromosomes are rare, occurring in approximately 1 in 25000 human fetuses ⁽²⁷⁾. A ring chromosome, which appears to be a rare event in cancer patients, can be formulated by fusions between both arms of the same chromosome with or without loss of genetic material. Ring chromosome structure is relatively conserved ⁽²⁸⁾ considering that ring chromosomes are rare in acute myelogenous leukemia (AML) ⁽²⁹⁾. Ring chromosome with deletion 7q in acute myeloid leukemia also reported from India ⁽³⁰⁾ and Ring chromosome 5 in acute myeloid leukemia defined by whole-genome single nucleotide polymorphism array ⁽³¹⁾.

Ring chromosomes are rare cytogenetic abnormalities that occur in less than 10% of hematopoietic malignancies but have been reported in up to 70% of mesenchymal tumors ⁽²⁶⁾. However, there are rare, recurrent cytogenetic abnormalities in AML that have not been classified. This is primarily due to the small number of reported patients, whose risk category and response to treatment is not well known. In patients with hematopoietic malignancies, ring chromosomes are commonly part of a complex karyotype ⁽²⁹⁾. Ring chromosomes come to clinical attention either in association with developmental anomalies at the beginning of life or with telomere shortening in ageing and neoplastic cells. It is likely that a transition from a DNA-damage sensitive to a DNA-damage tolerant state explains the high instability of rings in some tumor cells compared to those in non-neoplastic cells. However, many tumors show a pattern similar to that of normal cells.

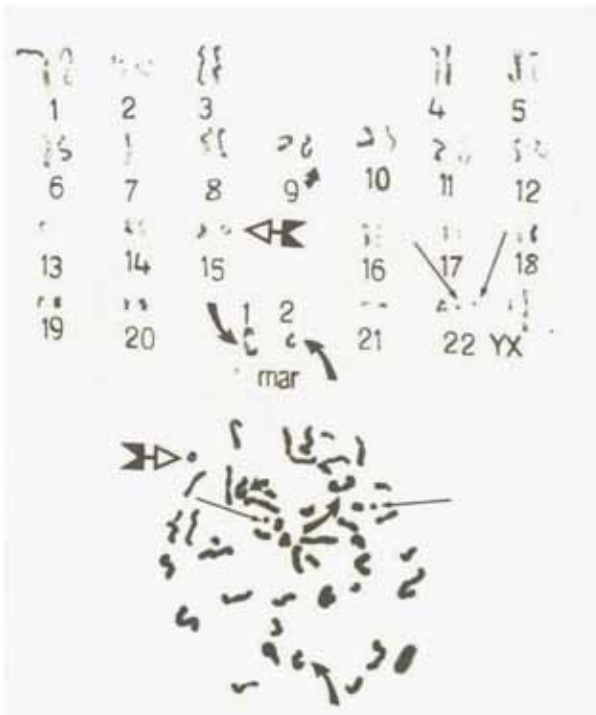


Figure 4 : Double Philadelphia chromosome apparently ring 15 and two unidentified marker chromosomes in the case of accelerated chronic myeloid leukemia.



Figure 5 : Ring and Philadelphia chromosome in at least 10% the total cells at the initial presentation.

One might tentatively distinguish two main modes for chromosomal reorganization in tumors. These are as type 1 and 2.

Type 1: Where simple chromosome rearrangements lead to either the formation of a chimaeric gene or a dysregulated oncogene expression with potent transforming capability. The BCR / ABL1D: 1> fusion in chronic myeloid leukemia and the EWS / FLI1 fusions in are examples of this mode. In general, such tumors show few additional chromosomal abnormalities and ring and dicentric chromosomes are rare.

Type 2: Where vast chromosomal instability lead to formation of complex karyotypes and multiple gene changes including activation of oncogenes and loss of tumor suppresser genes. This mechanism of constant chromosome evolution most probably acts against a background of disrupted DNA damage and/or mitotic checkpoints⁽¹⁴⁾. It is common in many aggressive solid tumors, e.g. lung cancer, ovarian carcinoma, pancreatic carcinoma, and a number of sarcomas.

In Type 1 lesions and non-neoplastic cells, ring chromosome structure is relatively conserved: rings may be duplicated or lost, but structural rearrangements are rarely maintained in the cell population⁽⁸⁾. In Type 2 lesions, rings show extensive structural variability and provide a means for gene amplification. Ring chromosomes are thus illustrative proofs that chromosomal behavior is not only a function of straightforward molecular interactions; chromosomal topology and the physiological context in which a certain chromosome aberration occurs must also be taken into consideration.

Ring chromosome are cytogenetic hallmarks that might be useful in determining a proper diagnosis^(32,33). The structure and formation of rings in tumors and leukemia have been poorly investigated. The reason for this might be that acquired rings are often difficult to characterize by chromosome banding techniques owing to the complexity of rearrangements, suboptimal banding quality, and shortage of material. The cytogenetic delineation of ring chromosomes is further complicated by their structural instability^(10,11).

Conclusion

To our knowledge, this case is the first finding of apparently ring chromosome 15 presented here confirms the value of cytogenetic analysis in characterizing the malignant clone in hematological neoplasia. This finding, together with the accumulated data in the literature, needs more research work to resolve diagnosis and therapy for further firm conclusion.

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Authors' Contribution

This work was written in collaboration with all the authors. Finally, all authors have read and approved the final manuscript.

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