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ORIGINAL RESEARCH

Detection of Sole and Clonal Aneuploidy in Hematologic Malignant Diseases

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ABSTRACT
Numerical chromosomal aneuploidy has diagnostic and prognostic value in detection of cancer. Hence, the study was undertaken in leukemic cases in our diagnostic laboratory. Analysis of 211 leukemic blood samples from referral cases of Neuberg Supratech Referral Laboratory (NSRL), Ahmedabad, India, since 2017 to 2019 using WHO protocols for chromosomal study. Detection of 23 cases were obtained (23/ 211: 11%) with this condition. Trisomy 8, 11, 13, 21 and monosomy 7 contributed to 18 cases (18/ 23; 78%) with 5 clonal anomaly (5/23; 22%). Four clonal patients were +8, +21 and +21, XXY and -7 with XY cells. Another karyotype with 48,XY,+8,+19/ 47,XY,+8 was detected which seems to be a new cytogenetic anomaly in the literature causing haematologic neoplasms in this cohort.

KEYWORDS: *Aneuploidy, Karyotype, Haematologic neoplasms, Clonal anomaly, Blood*

INTRODUCTION

Cancer is one of the dreadful diseases around the globe including India. Blood cancer is one of them. It is caused by several factors including food, stress, age, sex and life styles including genetic factors like mutations, chromosomes number(s) with respect to polyploidy and aneuploid conditions in tissue and blood (Heim and Mitelman, 1995; Barch et al., 1997; Arsham et al., 2017). Aneuploidy is a condition that leads to loss/ deletion or addition/gain of a chromosome with respect to particular set(s). This chromosomal condition creates a variety of cancers in blood (Rajasekhar et al., 2013). Leukemic cancers are mainly of two types; myeloid and lymphoid diseases of malignancy like acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL) etc. ALL is usually caused by gaining of chromosomes and by relatively few structural abnormalities. Certain most common sole trisomies include +4, +6, +10, +14, +17, +18, +20, +21 and X. Chromosome 21 present in 100% of cases frequently is tetrasomic (Williams et al., 1986). B cell chronic lymphoblastic leukemia (CLL) has trisomy 12 in most of the cases (Mitelman et al., 1994). In other lympho profliferative disorders, a gain of chromosome 8, 19, Ph+ were noticed, in addition loss of 7, 17, 8, Y with Philadelphia chromosome (Ph+). Other structural rearrangements were also seen (Barch et al., 1997;

Arsham et al., 2017). Several laboratories show clonal chromosomal abnormalities in 40-70% of bone marrow (BM) cells in MDS cases. These include +8, -5 or -7 and their deletions. The patients with MDS have single/ multiple chromosomal changes. Chromosomal changes in polycythemia vera (PCV) include gain of 8 or 9 chromosomes and other structural rearrangements (Rowley and Testa, 1982; Swolin et al., 1988; Mitelman et al., 1994; Heim and Mitelman, 1995).

Hence, this work was undertaken in our Diagnostic Laboratories, Ahemadabad for detection of sole aneuploidies and clonal types in referral cases since March 2017- April 2019.

RESULTS AND DISCUSSION

Numeric chromosomal aberrations are important as their frequency is essential for causing varieties of homologic malagnancies. We detected 23 chromosomal aneuploidies in our cancer cases from 211 referrals (23/211= 11%) with clonal frequency of (5/23=22%, Table-1; Fig.1). Gain of sole chromosome 8 in 5 cases in our report indicated the CML with acute phase (Table-1). Rowley and Testa, 1982; obtained 119 patients in gaining of chromosome 8.

Table 1: Aneuploidy with cancer cases (23) in our referrals (211)

Age (yrs)	Karyotype	Condition
30 - 74	45,XX, -7 (8)	Monosomy 7
35	47,XX,+21 (1)	Trisomy 21
34	47,XX,+11 (1)	Trisomy 11
74	47,XY,+11 (1)	Trisomy 11
35 - 74	47,XY,+8 (5)	Trisomy 8
50	47,XY,+13 (1)	Trisomy 13
57	45,XY, -7 (1)	Monosomy 7
88	46,XY[3]/47,XY,+8 [12]	Mos. with Trisomy 8
67	46,XY[4]/45,XY, 7-[11]	Mos. with Monosomy 7
60	46,XY[4]/47,XXY [11]	Mos. with KSS
30	46,XY[3]/48,XY,+21,+21 [12]	Mos. with tetrasomy 21
85	47,XY,+8[5]/48,XY,+8,+19 [15]	Mos. with Double T8,19 & T8.

Numbers in square bracket indicate number of cells analyzed; numbers in bracket refer to cases.
Total Percent: 23/211=11%
Mosaics (Males only)=05 ; Mos=Mosaic

Fig 1: Numerical Chromosomal anomalies in study cases (23)

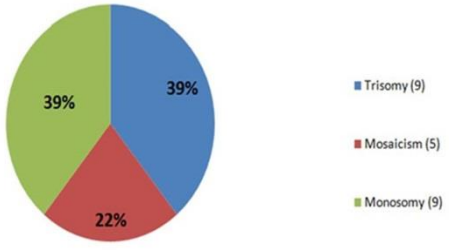

Figure 1: Numerical Chromosomal anomalies in study cases (23)

The extra chromosome 8, a recurring numerical chromosomal aberration in acute myeloid leukemia (AML) is known. It occurs either as a sole anomaly or with other aberrations (Vaniawala et al., 2017). It can be one of the prognostic values in cancer. Similarly Bakshi et al., (2012) described the clinical impact of T8 on carcinogenic progression. Its role in AML, MDS and other cancer types has been suggested (Mertens et al., 1991). These studies along with our result further support the role of sole T8 in cancer progression along-with others as cited above.

The frequency of chromosome loss in the acute phase is also low. Only 8 patients with loss of chromosome 7 were noticed (Barch et al., 1997). Our report also however detected good number of patients with monosomy 7 (9/23 = 39%). Myelodysplastic syndromes (MDS) are heterogenous leukemic disorders related to

various degrees of myelosupression and transformation into acute leukemia. Chromosome 7 anomalies occur at any age, have several disease association with ineffective hematopoiesis, dysplastic changes in blood and BM progressing to AML (Bacher et al., 2015; Cordoba et al., 2011). It is usually related to old age and also ranged from 50-74 yrs in our cohort. Familial monosomy 7 too is reported in early childhood on-set in a minority of individuals with bone marrow failure as a sole anomaly (Morrisette et al., 2016) This could be due to environmental factors, treatment, age and others. Females were (8 cases) more too in this study (Table-1). Thus our data explained out of 23 cancer cases maximum number of patients detected in this study cohort were of MDS/ AML with sole aneuploidy of +8 and -7 (14/23; Table-1). Further two cases of trisomy 11 are related with primary/ secondary MDS, progressive to AML having age 37 and 74 yrs detected. A case with T11 solely detected by Yoo et al., 2017 transforming to chronic myelomonocytic leukemia (CMML) was reported. It is classified as one of the myelodysplastic and myeloproferative disorders (MDSs/MPNs) by WHO Yoo et al. (2017). Isolated trisomy-11 in de-novo AML and its mechanism between trisomies and leukemogenesis remain unknown and more information about this connection is essential (Krum et al., 2008). Besides T11, abnormalities related chromosome 11 translocations, interstitial deletions and duplications are reported with various hematological disorders. Similarly +13 also defines a homogenous AML and is highly associated with high frequency of mutations in spliceosome genes and poor prognosis(Herold et al., 2012). Constitutional aneuploidy is linked to increased cancer risk. Isolated sole T13 (Patau's Syndrome) is a severe congenital disorder with cerebral, cardiac and renal formations. It is also related to solid neoplasms including neuroblastoma and nephroblastoma (Herold et al., 2012). In our study a case with T13 with 50 yrs male was noticed having a sole chromosomal anomaly in support of Herold et al. (2012). He documented 34 patients with AML T13 positive. Trisomy 21 as a sole chromosomal abnormality in AML was shown by FISH and spectral karyotyping Ohsaka et al. (2002). Guo et al. (2004); notified aplastic anemia proceeding AML-MS occurring 14 yrs following a successful treatment to anemia with clonal anomaly, 47,XX,+21(10)/ 46,XX(1) in a case. A unique cytogenetic finding in T-cell ALL with +21 was reported (Rizvi et al., 2017). The incidence of T-cell ALL accounts 20% of the population (Rizvi et al., 2017). Our case of T21 needs to be further investigated having 35 years with no Down symptoms.

Five clonal anomalies were detected in males (5/23) which are +8,-7,XXY and tetrasomy 21 with normal XY cells and T8,T19 with T8 (Table-1; Fig.1). Monosomy 7 with one chromosomal anomaly is encountered in 14% cases (Al-Anazi et al., 2016) while describing MDS disorders. Chromosome analysis of the bone marrow of a 50 year old female patient presented karyotype of 49,XX,+1,+8+21 (16) with four normal XX cells showing clonal anomaly with 8 (Abdelrahman et al., 2016). Potocki et al. (1994); with direct preparation and unstimulated 24 hr culture of BM were found to be 19/21 cells with 48,XX,+21,+21 and two cells with 46,XX. On cytogenetic study of PHA stimulated 72 hr PBLC, 16 of 21 cells were 46,XX [11] and 5 were 48,XX,+21,+21. The former is a normal constitutional compliment of tetrasomy +21 chromosomes (Potocki et al., 2004). Our case is from leukemic blood with 30 yrs of an opposite sex with clonal compliment of 46,XY (3) and 46,XY,+21,+21 (12.) The clonal cases of +8 and -7 with normal XY cells indicated an increased risk of hematologic diseases (Godze et al., 2016; Arsham et al., 2017). Swerdlow et al. (2005); identified cancer incidence and mortality in men with clonal anomaly of Klinefelters'syndrome (KS). Sanctis et al. (2013); attributed in majority of cases the karyotype is 47,XXY; however variant syndromes such as 47,XXY and mosaicism (47,XXY/46,XY) account for 20% of cases which occur from childhood to adulthood. In our study, the case had 60 yrs with clonal anomaly with 46,XY(4)/ 49,XXY with multiple reproductive abnormalities (Table-1).

In our cohort study, a case with clonal chromosome compliment of T8 (5) and T8,T19 (15) were identified in blood of male client with 85 years old which had abnormal karyotype (Table1; Fig.2). Out of 20 cells analyzed this condition indicated MDS of

myeloproliferative malignant neoplasms. This new clonal compliment case needs further investigations in future, although +8 and +19 sole anomaly cases with these proliferative disorders (Daskalos et al., 2006; Vaniawala and Godhia, 2012; Jung et al et al., 2017) were detected. Thus our case requires more studies with FISH probes and hematological analysis to confirm this clonal anomaly. Such a clonal anomaly seems to be a new abnormal clonal compliment in leukemic neoplasms in the literature.

Figure 2: Clonal anomaly in our study

CONCLUSION

The numerical aneuploidy in our hematologic malignant cases from our centre helped to detect trisomy 8, 11, 13, 21 and monosomy 7 respectively followed by 5 clonal anomalies (23/211=11%). A case with clonal anomaly, of 48,XY,+8,+19[5]/ 47,XY,+8[5] is a new cytogenetic investigation, related to myeloproliferative condition as far as our knowledge is concerned. More studies are underway in this regard for confirmation.

MATERIALS AND METHODS

A number of 211 referral cases were analyzed using their blood samples (5ml/sample). These patients were asked to fill the relevant consent forms and instructions were given before sample collection. The blood of cancerous type was used for chromosomal analysis following the method of WHO protocols (Jordan et al., 2016). Fifteen to twenty metaphase plates were analyzed for chromosomal studies. Only chromosomal gain/ loss and mosaicism were evaluated and percentage were also calculated. This study was approved by the ethics committee of Gujarat University, Ahmedabad.

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