Research Article

Cytogenetics abnormalities in acute leukemias of ambiguous lineage: First report of complex variant philadelphia translocations

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Abstract

Background: Acute leukemias of ambiguous lineage (ALAL) are incompletely characterized and are very rare, accounts< 4% of acute leukemias . In most leukaemias the cytogenetic and molecular genetic changes have emerged to be diagnostic as well as prognostic importance. Due to Lack of diagnostic criterias, it is difficult to establish cytogenetic features in ALAL. In present study we reviewed chromosomal aberrations, their molecular background, their prognostic relevance of ALAL & summarized some new chromosome aberrations along with probable mechanism of complex variant translocation. **Design and Methods**: Present study from Kidwai state cancer institute concentrated on cytogenetic findings of ALAL, especially B+Myeloid MPAL cases, more so regarding complex variant phildelphia chromosome translocations summarised diagnostic criteria based on WHO 2008 classification, clinical, immunophenotyping and molecular features, along with treatment & follow up. **Results**: Among 32 cases of ALAL cases, 28 MPAL cases reported in the present study 13 cases were B/Myeloid, followed by B+T MPAL, T+Myeloid. 4 cases of undifferentiated and unclassifiable leukemias were reported. B/myeloid MPAL were in majority, 13 cases. Cytogenetics abnormality was detected in 4 cases of B/myeloid MPAL. 3 cases were Ph +, another case was hyperdiploid, surprisingly out of 3 Ph+ cases, 2 cases (66.6%) showed complex variant Phildelphia chromosome. **Conclusion**: B+MYELOID MPAL revealed significant cytogenetic abnormalities. Although Ph+ is reported in MPAL, complex variant Ph with 4 or 3 way translocations are not reported in ALAL especially in B/Myeloid MPAL. Immunophenotyping & cytogenetics in ALAL should be mandatory. Multiple levels of genetic heterogeneity exist in these leukemias with variant Ph translocations. Prognosis improves when treated with Imatinib

Keywords: Mixed phenotypic acute leukemia, Cytogenetics, Complex variant Phildelphia translocations, MCP841protocol, B/Myeloid.

Introduction

The cytogenetic testing of MPAL is of paramount importance as it can confirm the diagnosis, determine treatment options and provide prognostic information, when specific chromosomal abnormalities is known. Initial karyotype at presentation involving either chromosomal rearrangement with known prognosis or unknown prognosis constitutes an independent determinant for complete remission & risk of relapse [1]. Present article focuses on ALAL, the importance of cytogenetic analysis, especially in B/Myeloid MPAL, supporting the importance of karyotyping in the disease pathogenesis, diagnosis, prognosis, treatment & follow up. Present article reviews in detail the types of chromosomal aberrations, their molecular background, probable mechanism of complex translocation & their prognostic relevance. It also summarizes some new chromosome aberrations that have been reported only once, it also highlights the future research aspect on ALAL in the branch of cytogenetics. t (9;22), (q34;q11) leading to formation of BCR-ABL1 fusion gene, accounts for <1% of acute leukemias [2], however occurs frequently in MPAL. About 5-10% of CML patients have complex variant translocations involving a

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third chromosome in addition to chromosome 9 & 22 [3,4].

To best of our knowledge complex variant translocations involving Ph chromosome in MPAL especially in B/Myeloid MPAL have not been reported in detail & Impact of these variant translocations, on prognosis has not elucidated. More studies in ALAL with variant Phildelphia might further clarify our findings

Material & Methods

Our laboratory received 1855 acute leukemias, during a period of 4 years from January 2012 to march 2016, where diagnostic flow cytometric analysis was done and leukemias were classified based on WHO 2008 criteria's.

ALAL was diagnosed in 32 patients. Out of these, 28 cases were MPAL. Study concentrated mainly on cytogenetic findings in13 cases of B+Myeloid MPAL cases.

G banding was done on over night-unstimulated cultures of bone marrow &were analysed. Conventional cytogenetic analysis was performed on BMA according to the standard cytogenetic methods. Unstimulated BMA was cultured for 24 and 48 hours in RPMI-1640 media supplemented with 15% Fetal bovin serum at 37C. The cells were exposed to colcemid (0.10 mg/ml) for 30 minutes after incubation, later treated by hypotonic treatment (0.075 M KCl) for 20 minutes and fixed by methanol and glacial acetic acid (3:1). The chromosomes were G- banded with trypsin, Giemsa stain and the karyotype was analysed.

Results

Among 32 ALAL cases diagnosed in 4 years in our institute, MPAL was diagnosed using WHO criteria in 28 patients (1.4 %). 4 cases were acute undifferentiated leukemias/unclassifiable leukemias. Among 28 MPAL cases, 13 cases were B+Myeloid MPAL (46%). Surprisingly only B+Myeloid MPAL showed most abnormal cytogenetic findings.

Baseline investigations revealed leucopenia in most cases of B/myeloid MPAL, 3 cases had increased total count (TC). All 3Ph+ MPAL were B/Myeloid MPAL cases and had increased total count, 2 cases had very high Total count, $100x10^9$ /L. All B/Myeloid MPAL cases had Thrombocytopenia including Ph +cases,Mean platelet count was $40x10^9$/L, meanHb was 8g/dl

Mean serum lactate dehydrogenase (LDH) was 941 IU/L, In all cases, serum alkaline phosphatase was within normal range and liver enzymes were found to be elevated in a single case. Serological studies for HIV, HBsAg and HCV were negative. Blasts percentage varied from 20% to 70% (Fig 4).

Fig- 1:P h + MPAL presenting with orbital mass.

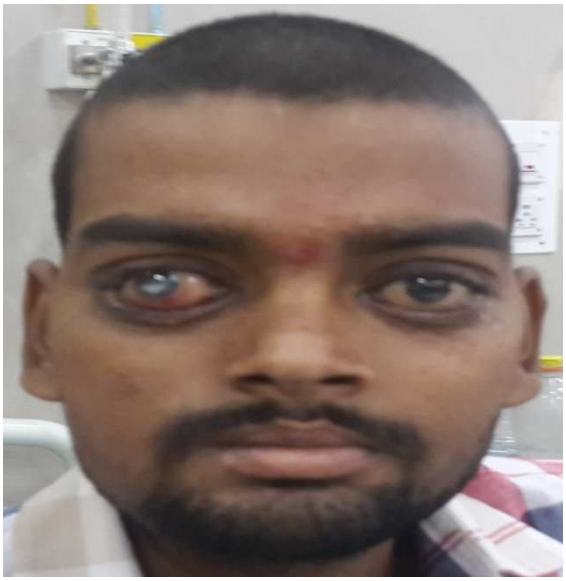

Fig-2: Ph + MPAL ,Resolved orbital mass ,post treatment

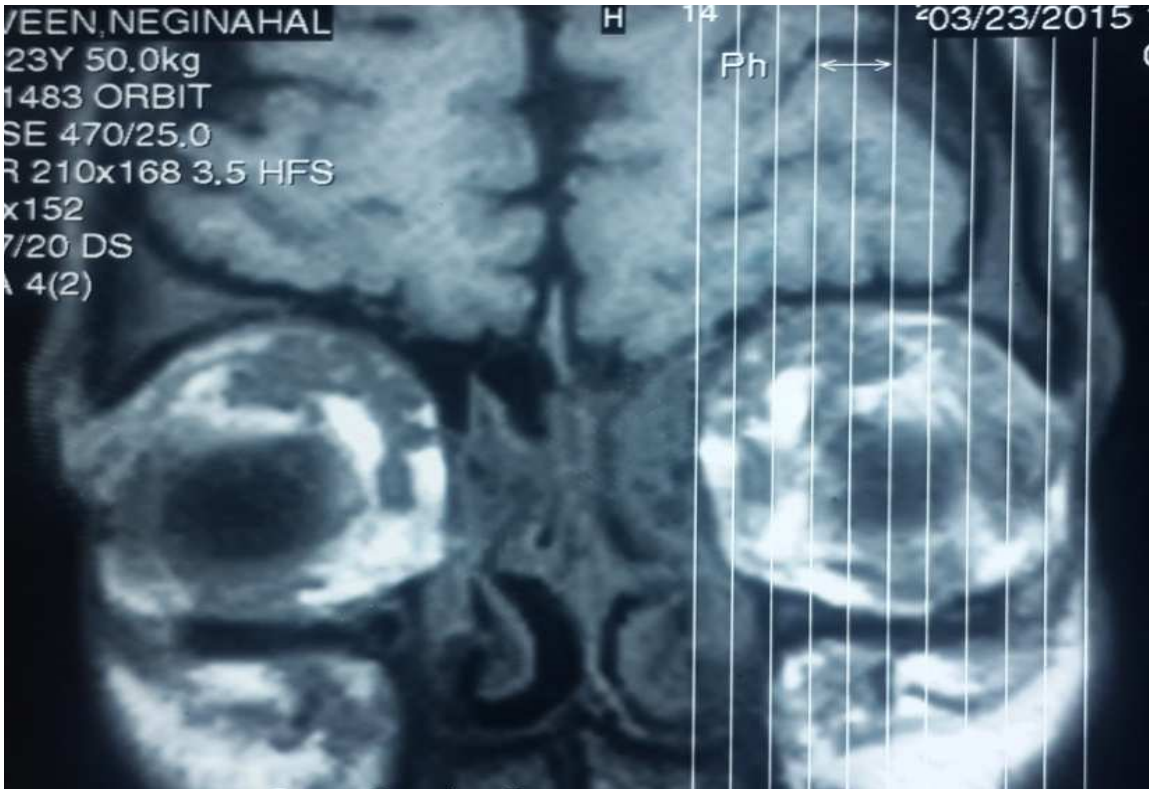

Fig-3: MRI plain showing Bilateral Orbital iso-intense lesions.

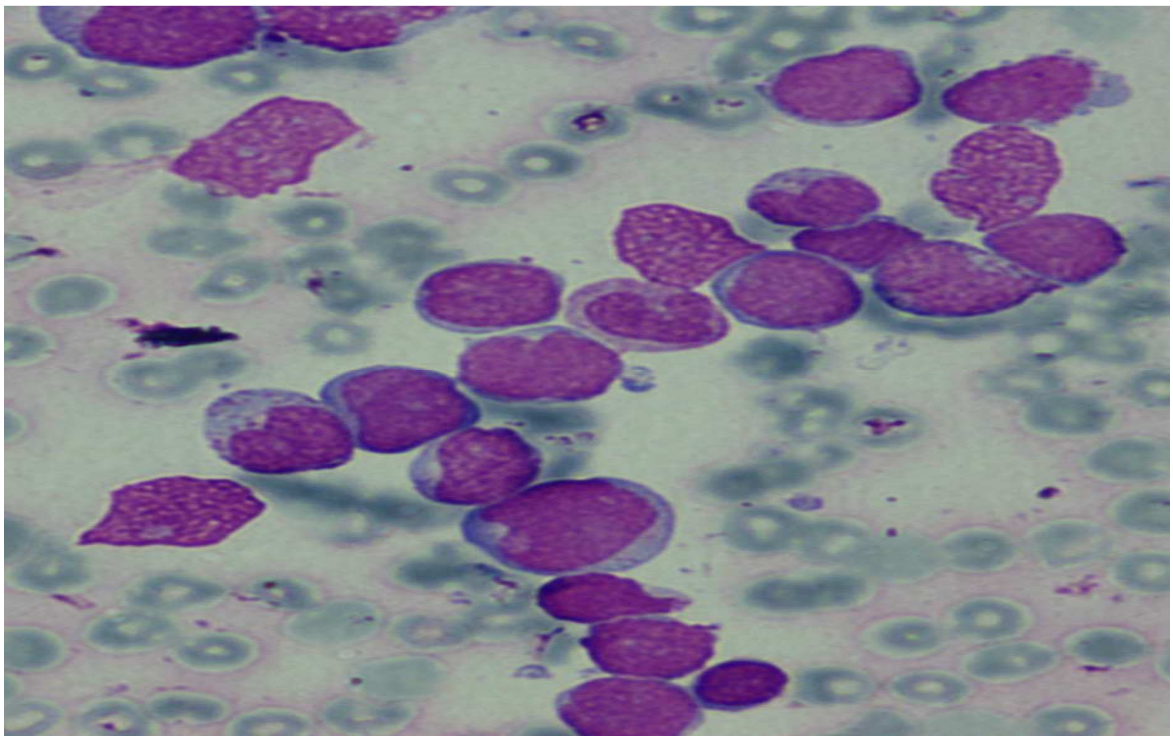

Fig-4: B/Myeloid MPAL showing blasts

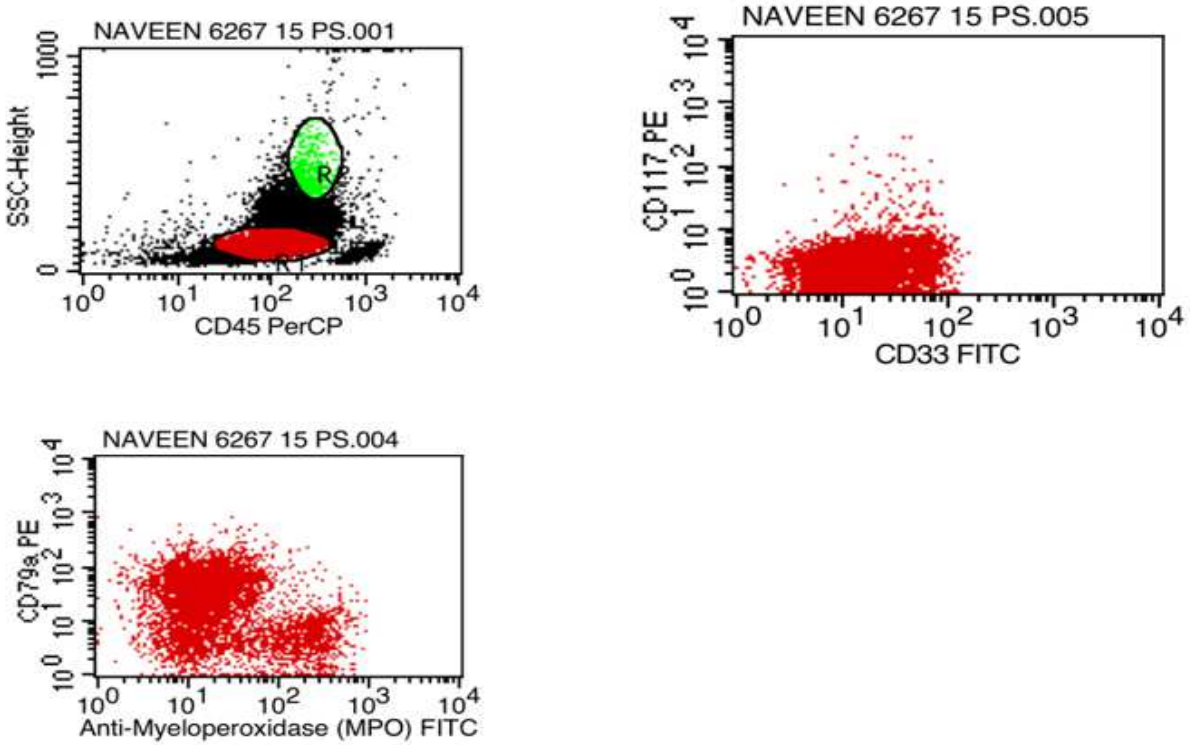

Fig- 5: Flow Scatterogram of B/MYELOID MPAL.

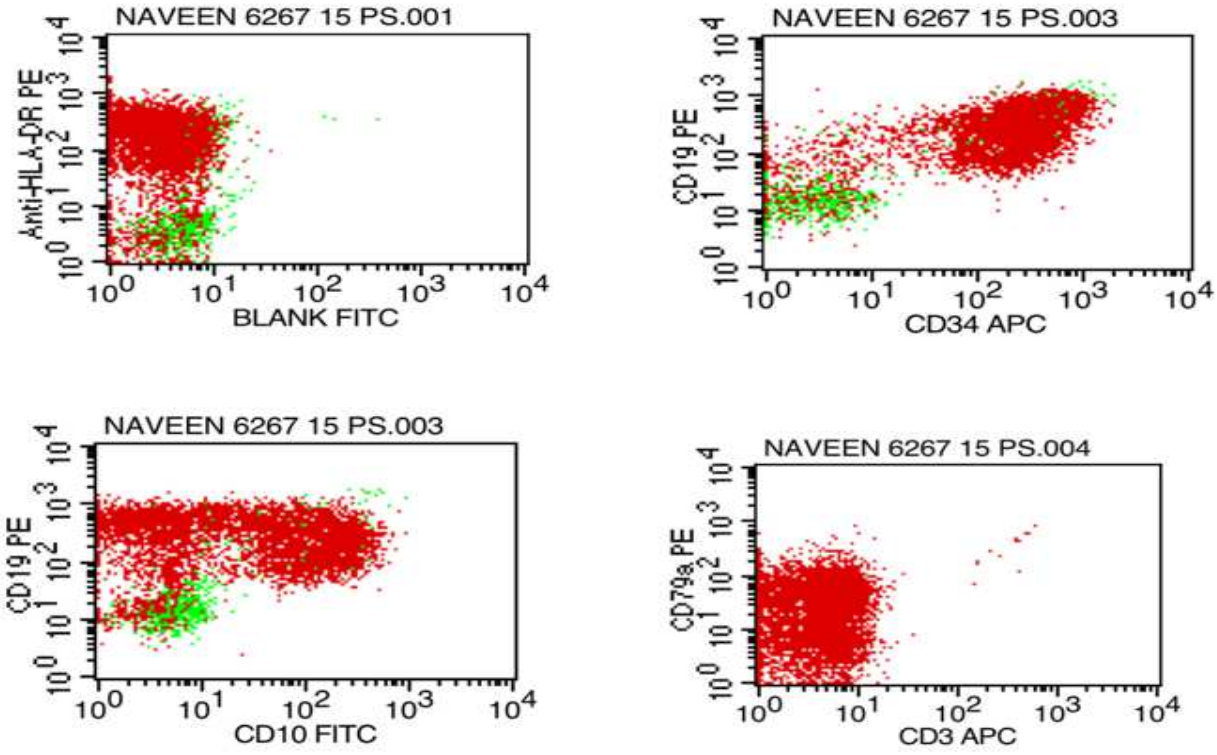

FIG-6: Flow Scatterogram of B/MYELOID MPAL

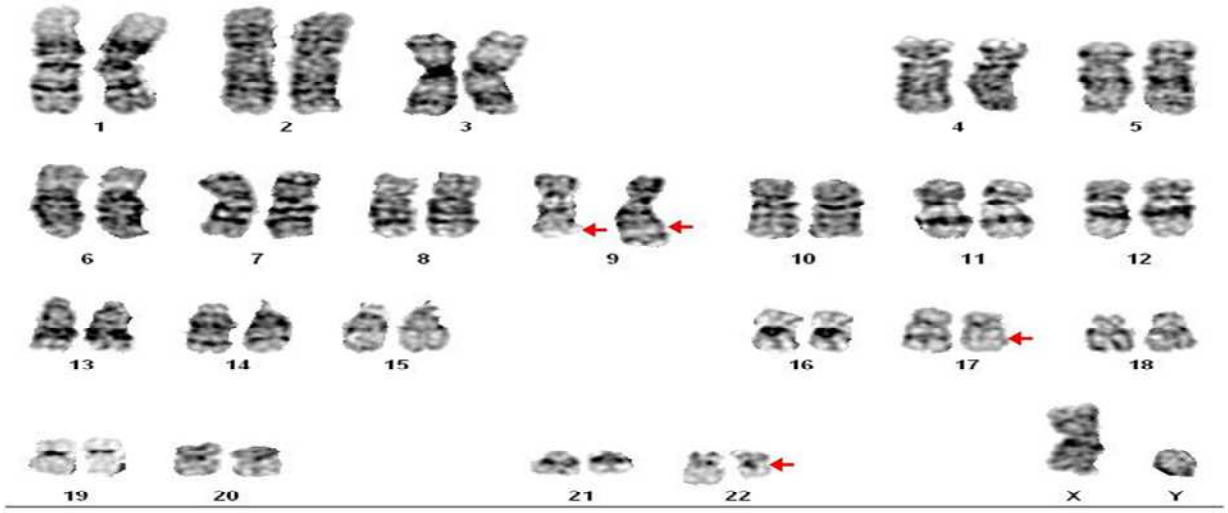

Fig-7: Complex Variant Phildelphia Chromosome Translocation 46XY,t(9;9;17;22)(q34;q22,q22,q11).

Marker of early hematopoietic cells, CD34, was strongly positive in 70 % cases. All cases were positive for both Myeloid & lymphoid markers, MPO, CD19 and CD 79a. CD13 & CD 33 was positive. CD117 & CD 10 was positive in 75 % of cases. (Fig 5 & 6) cytogenetic data was available in all 28 MPAL cases. Among 13 cases of B/myeloid MPAL cases, 4 case showed abnormal karyotype, one was hyperdiploid, 3 cases revealed Ph chromosome, First case was conventional Ph chromosome who presented as orbital mass (Fig 1 & 2), MRI Bilateral Orbital iso-intense lesionsnoted. (Fig 3) & 2 otherPh + cases had complex variant Phildelphia chromosome, t (7;9;22) (q11;q34;q11), and another case46XY, t (9;9;17;22) (q34,q22,q22,q11 (Fig 7). Single case of hyperdiploidy in B/T MPAL was noted. single adult AUL case revealed del (9) (q22).

RT PCR showed increased ABL/BCR, P210 fusion protein in all 3 Ph+cases, however none of the patient had spleen nor antecedent history of CML.

Discussion

In the majority of patients with acute leukemia, blast cells can be assigned to specific lineage, Myeloid, B Lymphoid or T-lymphoid. However, in 2-5% of patients, after immunophenotyping by flow cytometry (FCM), lineage of leukemias remains ambiguous [2].

When the blasts express more than one lineage antigens it is not possible to assign to any particular lineage, it is called MPAL. Immunophenotypically Mixed phenotype acute leukemia can be further sub classified as B/Myeloid, T/Myeloid, B/T, or trilineage based on immunophenotypic findings [2] .

The t(9;22), (q34;q11) resulting in the BCR-ABL1 fusion gene [2], accounts for <1% of acute leukemias. Ph + MPAL are very few, detailed study of these cytogenetic abnormalities especially complex variant Phildelphia chromosome in MPAL are unreported so far. Using the WHO 2008 criteria, MPAL shows a decreased frequency (0.5-2.8%) compared to EGIL system (2-5%). MPAL affects both adults and children & shows a male predominance. Reports on the outcome of patients with MPAL are few but it is believed that MPAL has poor prognosis, especially in adults and those with a Ph chromosome [5 & 6}. In most leukaemias the cytogenetic and molecular genetic changes have emerged to be of the greatest, in diagnosis and prognosis. However, the clinical, biological, prognostic factors and treatment stratifications in ALAL especially B/Myeloid MPAL have remained elusive due to its rarity and the lack of uniform diagnostic criteria [1].

Clonal chromosome abnormalities can be numerical (involving changes in chromosome number), or structural (including mainly translocations /deletions) or both. Cytogenetic analysis reveals clonal chromosomal abnormalities in 59-90% of MPAL patients .80-90% of patients with AUL also reveals clonal chromosomal abnormalities [1]. In present study ¼ case of AUL revealed cytogentic abnormality in the form del (9) (q22).

Cytogenetic analysis can detect chromosomal rearrangements across the whole genome.Initial karyotype at diagnosis involving, chromosomal rearrangement with known prognosis or unknown prognosis, is an independent determinant for attainment & duration of Complete Remission, risk of relapse and survival. New chromosome aberrations during the course of the disease could predict a upcoming relapse [1].

Immunophenotyping data showed, the predominant type of MPAL was B+MyeloidMPAL comprising 13 cases (46%), This is similarto the majority of thepublished studies where B+ Myeloid constitutes the predominating type of MPAL [2] however our study had majority 8 cases children, adults were only 5.

In MPAL, specific cytogenetic rearrangements have been identified and associated with distinct immunophenotypes, however t(8;21)(q22;q22) is excluded from MPAL according to WHO 2008 criteria [2].

Cytogenetic studies are absolutely essential in characterizing MPAL as they disclose poor prognosis.Ph + is the most frequent chromosomal aberration in MPAL, Prateek et al found incidence of MPAL cases was 6% & the BCR –ABL + was 40%. Studies from Asia by Xu et al, Lee et al & Mi et al found MPAL as 4.6%,2.1%, & 3.4% and BCR-ABL + as 25%, 36.8% and 16.7% respectively. Studies regarding the incidence of MPAL in West, by Killick et al, Legrend et al, carbonellaetal & Owaidah et al found 1.3%,3.6%,8%&4%.BCR-ABL+WAS18.8%,38%,35%, 30.8% &9% [9].

Commonly described cytogenetic groups in MPAL are, compelx karyotypes, t(9;22), (q34;q11) and t(v;11q23). Complex karyotype with 3 or more clonal chromosome abnormalities are observed in MPAL. Most common ly involved are del(7q),del (6q),del(5q),and del (17q). present study did not have any of these deletions [1]. t(9;22), (q34;q11) resulting in the BCR-ABL1 fusion gene, accounts for <1% of acute leukemias, however occurs frequently in MPAL. The great importance of cytogenetic abnormalities in MPAL was revealed by the fact the t(9;22) (q34;q11.2) and t(v;11q23) are considered as separate entities of MPAL as per to WHO 2008. Studies have also shown that Ph positivity and MLL gene rearrangement is an paramount risk factor for the survival and has a very bad prognosis [2].

Significant lower Incidence of Ph chromosome was noted in Paediatric MPAL (0-16%) [5,8 & 9}. Present study a single case of complex variant Ph with a 3 way translocation, was noted in a child & was B/Myeloid MPAL. In adults the Incidence of Ph chromosome is higher [1,10 & 11], we had 2 adults with Ph+, one was conventional Ph chromosome, who presented as orbital mas, other was a complex variant of Phchromosome,with a 4 way translocation. Complex Variant Phildelphia in CML have been described, but never ever in MPAL Similar to Atfy et al &Wang in 2011; Patients with Ph+ were predominantly male,we also had 2/3 (66%) Ph +cases in men. Total WBC count was high in these studies, In present study all 3Ph+ cases, including 2 complex variant Ph had high total count, 2 cases had very high Total count,$100x10^9$ /L. All 3 cases had Thrombocytopenia.

Study by Wang et al showed Ph + in most cases of B/myeloid MPAL[12], similar to his study Ph positive was seen exclusively in B/myeloid MPAL.All cases reported either the t(9;22), that is Phildelphia chromosome positive, is detected by karyotype,or the BCR-ABL1 fusion gene detected by Fish or PCR. Present study all 3 cases had Ph on conventional karyotype, also Abl/Bcr (p210) transcripts were noted on RT PCR, however had none of these had prior history of CML, nor a huge spleen, had very short history.

Variant phildelphia translocations in CML account for up to 10%. By conventional cytogenetic analysis two variant sub groups have been recognized:complex, t (9:22:v), third translocation partner chromosome is represented as V;andsimple, t(9:v) or t(22v) [3,4].

The BCR-ABL fusion is detectable in both these groups,on the Ph chromosome or occasionally on the additional translocation partner [13,14,15]. variant Ph translocations can involve any chromosome, however,marked clustering has been observed to some bands, notably 3p21, 3q21, 6p21, 11q13, 12p13, 17q21, 17q25 & 22q13 [3,4]. Some reports have observed that most recurring breakpoints occur in the region of recognized oncogenes,fragile sites or typical secondary breakpoints in other malignancies [16,17], no study has been published in which molecular methods have confirmed these speculations.

The mechanism by which variant Phildelphia translocation takes its origin is controversial issue. fitzgerald and morris as proposed two possible mechanism: the first is a single event rearrangement via

the simultaneous breakage of many chromosomes followed by joining of mismatched portions of chromosomes. The second involves two serial translocations;a conventional Ph, later followed by a translocation between chromosome 9 & 22 and a third chromosome.evidence in support of the two step mechanism includes reports of a few patients, where cytogenetic evolution from a classical Ph to variant was noted [18]. Calabrese et al claimed to have found evidence of this two step process by identifying portion of chromosome 22 present on the der (9) chromosome, which was detectable by FISH, in 9/10 variant CML. other studies however have failed to support these findings [19,20,21].

We had for the first time complex variant translocation a 3 way translocation, t(7;9;22) (q11;q34;q11) in a 14 year girl. Similar translocation is earlier reported by reid et al, but that was in CML. A conventional Ph + in a 23 year old male and a complex variant translocation, a 4 way translocation, for the first time in MPAL t(9;9;17;22) (q34;q22;q2q11) in a35 year old male.

Reid et al in 2003 has studied extensively 54 cases of variant phildelphia translocation, however it was in CML[20]. Ph + MPAL either can have p190 transcript or p210 transcripts [1,7], in present study we had all 3 cases with b3a2 (p210) transcript. Recurrent cytogenetic abnormalities observed in MPAL are trisomies 19, 21, and hyperdiploidy. We had 2 cases with hyperdiploidy, one case was B/T MPAL & Other was B/Myeloid MPAL.

The mechanism of formation of a variant Ph translocation may have clinical relevance;a two event mechanism may represent clonal evolution,where as a variant translocation via a single genomic rearrangement may confer a similar prognosis to the conventional Ph translocation. Previous analysis of variant Ph positive CML, however have yielded contradictory results. Many reports have noted worse prognosis in variant Ph-positive cases than in those with conventional t (9;22), but other studies have failed to support this theory. few studies have established shorter survival due to increased frequency of derivative chromosome 9 deletion [20].

Decreased survival was noted in variant Ph patients than in those with the classical Ph translocation in pre imatinib era, due to deletion of the derivative chromosome 9 were found in higher frequency in patients with variant translocations than with the conventional t(9;22) (q34;q22) translocation [22,23]. Acute undifferentiated leukemia are diagnosed when the blasts exhibit no lineage-specific antigens [2]. Acute undifferentiated leukaemia seems to be more common in older adults [1], we had 4cases of AUL, 2 in children, one was 2 yr old & other was 14 year old. single adult case revealed del (9) (q22) .

Cytogenetic analysis reveals clonal chromosomal abnormalities in 80-90% of patients with AUL.AUL shows a high frequency of del (5q) and trisomy 13 [10,11]. The prognosis of AUL patients is poor .1 out of 4 cases of AUL in present study, had cytogenetic abnormalities on conventional karyotyping.

Incidence of a complex variant of Ph chromosome in MPAL is not described. In present study variant Ph was much more frequently seen than conventional Ph+, 2/13 cases B/Myeloid MPAL (15 %), this could be attributed to small number of Ph + patients in the study. Further studies are essential in this rare disease, to clarify whether complex variant translocations common in B/Myeloid MPAL. Few frequently seen cytogenetic abnormalities in MPAL, especially in B/Myeloid MPAL are Del(1)(p32); Deletion of chromosome I involving the p32 locus (del(1) (p32) affecting STIL-TAL1 fusion gene,Trisomy 8, Trisomy 4, Deletion of 16q, abn (7p); abnormalities of 7p including del (7p), del5q etc [1,6]

Although the prognostic importance of few chromosome abnormalities has been established, majority of chromosomal abnormalities has not been determined, this could be due to relative rarity of the disease, the different scoring systems proposed and the different treatment protocols used in many study groups. In a recent study of 21 Ph+ patients treatment outcome was poor with a year survival of 28%, & relapse free survival of 18% [1].

Our patients were treated with Imatinib& chemotherapy. Though all our Ph + cases including Ph variant chromosome attained remission, one adult patient who presented as orbital mass ,relapsed after 10 months and did not survive. Paediatric variant Ph+ child was referred to higher center for BMT after remission , adult Ph+variant patient is in remission and currently on follow up. It has been observed that patients with variant translocations have similar prognosis to those with classical t(9;22) (q34;q22) when treated with Imatinib [22,23,24]. All Ph+, whether conventional or variant Ph, responds well for Imatinib and

chemotherapy. More studies in variant Ph+ B/Myeloid MPAL might further clarify our findings

Novel genomic technologies, such as next-generation sequencing, may help to define the leukemogenic mechanisms in B/Myeloid MPAL cases and to determine a standardized treatment for these rare leukemias. Analysis of cytogenetics should be mandatory in these leukemias as they are increasingly important as potential targets for therapy in future. Presence of the Phildelphia chromosome should be checked always as it affects the treatment.

Moreover, molecular studies of structural chromosomal abnormalities, identified by karyotype may aid in the cloning of genes situated at chromosomal breakpoints and aid in characterizing the proteins involved in the genesis of leukemia[1]. Knowledge of these proteins may open new therapeutic ways in ALAL.

To best of our knowledge complex variant translocations involving Ph chromosome in MPAL especially in B/Myeloid MPAL have not been reported in detail so far& prognostic impact of these variant translocations has not been fully elucidated in B/Myeloid MPAL.More studies in variant Ph+ B/Myeloid MPAL might further clarify our findings

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Permission from IRB: Yes

References

1. KalliopiN. Manola. Cytogenetic abnormalities in acute leukaemia of ambiguous lineage: an overview. British Journal of Haematology.2013; 163, 24-39 DOI10.1111/bjh. 12484

2. Borowitz M J Bene MC,HarrisNL,PorwitA,Matutes E Acute leukemia of ambiguous lineage :WHO classification of hematopoietic and lymphoid tissue 4th ed.IARC,Lyon,France:2008.p 150-55.

3. Huret JL. Complex translocations, simple variant translocations and Ph-negative cases in chronic myelogenous leukaemia. Hum Genet. 1990 Oct;85(6):565-8.

4. Milelman, F The cytogenetic scenario of chronic myeloid leukemia. Leukemia and Lymphoma.1993; 11:11-15.

5. Al-Seraihy, A.S., Owaidah, T.M., Ayas, M., El-Solh, H., Al-Mahr, M., Al-Ahmari, A. &Belgaumi, A.F. Clinical characteristics and outcome of children with biphenotypic acute leukaemia. Haematologica, 2009;94:1682-90.

6. Matutes, E., Pickl, W.F., Van't Veer M., Morilla, R., Swansbury, J., Strobl, H., Attarbaschi, A., Hopfinger, (i., Ashley, S., Bene, M.C., Porwit, A., Orfao, A., Lemez, P., Schabath, R. & Ludwig, W.D. Mixed-phenotype acute leukaemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification, Blood.2011;117: 3163-71.

7. Prateek Bhatia, JogeshwarBinota, Neelam Varma, Deepak Bansal, AmitaTrehan, Ram Kumar Marwaha, Pankaj Malhotra and Subhash Varma.A Study on the Expression of BCR-ABL Transcript in Mixed Phenotype Acute Leukemia (MPAL) Cases Using the Reverse Transcriptase Polymerase Reaction Assay (RT-PCR) and its Correlation with Hematological Remission Status Post Initial Induction Therapy. Mediterr J Hematol Infect Dis 2012;4(1): e2012024, DOI 10.4084/MJHID. 2012,024.

8. Gerr, H., Zimmermann, M., Schrappe, M., Dworzak, M., Ludwig, W.D., Bradtke, J., Moericke. A., Schabath, R., Creutzig, U. & Reinhardt, D.Acute leukaemias of ambiguous lineage in children: characterization, prognosis and therapy recommdendations. British Journal of Haematology,2010; 149: 84-92.

9. Park, T.S., Lee, S.T., Song, J., Lee, K.A., Kim, J., Park, Y., Song,S. & Choi, J.R. Biphenotypic acute leukaemia with b2a2 fusion transcript and trisomy 21.Cancer Genetics and Cytogenetics.2009b; 188:129-131.

10. Cuneo, A., Ferrant, A., Michaux, J.L., Bosly, A., Chatelain, B., Stul, M., Dal Cin, P., Dierlamm, J., Cassiman, J.J., Hossfeld, D.K., Castoldi, G. & Van den Berghe, H. Cytogenetic and clinicobiological features of acute leukaemia with stem cell phenotype: study of nine cases. Cancer Genetics and Cytogenetics,1996; 92: 31-36.

11. Heesch, SNeumannschwartz, s, bartram, Schlee. c, Burmeister, T, Hanel etal Acute leukemias of Ambiguous lineage in adults:moiecular and clinical characterization.Annals of Hematology.2013;92:747-58.

12. Wang, Y., Gu, M., Y., Qiu, L., Bian, S. & Wang. J. Clinical characteristics and outcomes of mixed phenotype acute leukaemia with Philadelphia chromosome positive and/or bcr-abl positive in adult. International Journal of Hematology.2011; 94: 552-55.

13. Hagemeijer, A., Bartram, C.R., E.M., van Agthoven, A.J. &Bootsma. D. Is the chromosomal region 9q34 always involved in variants of the Ph1 translocation? Cancer Genetics and Cytogenetics. 1984;13:1-16.

14. Morris, C.M., Rosman, I., Archer, S.A., Cohranse, J.M. & Fitzgerald, P.H. A cytogenetic and molecular analysis of five variant Philadelphia translocations in chronic myeloid leukemia. Cancer Genetics and Cytogenetics 1988;35: 179-197.

15. Sessarego, M., Fugazza, G., Bruzzone, R., Ballestrero, A., Miglino, M. &Bacigalupo, A. Complex chromosome rearrangements may locate the bcr/abl fusion gene sites other than 22q11. Haematologica, 2000;85:35-39.

16. Heim, S., Billstrom, R., Kristoffersson, U., Mandahl, N., Strombeck, B. &Mitelman, F.Variant Ph translocations in chronic myeloid leukemia.Cancer Genetics and Cytogenetics. 1985;18:215-227.

17. Huret, J.L. &Tanzer.J. Non-random aberrant breakpoints in chronic myelogenous leukaemia revisited. A call for a collaborative study. Human Genetics.1989; 83: 208.

18. Fitzgerald, P.H. & Morris, C.M. Complex chromosomal translocations in the Philadelphia chromosome leukemias. Serial translocations or a concerted genomic rearrangement?Cancer genetics and Cytogenetics.1991; 57: 143-151.

19. Calbrese, G., Stuppia, L., Franchi, P.G.,Peila, R., Morisio, E., Liberati, A.M., Spadano, A., Di Lorenso, R., Donti, E. &Antonucci, A. Complex translocations of the Ph chromosome and Ph negative CML arise from similar mechanisms, as evidenced by FISH analysis. Cancer Genetics and Cytogenetics (1994); 78:153-9.

20. AlistaigG.Reid, Brian J.P. Huntly, Colin Grace, Anthony R. Green and Elisabeth P. Nacheva. Survival implications of molecular heterogeneity in variant Philadelphia-positive chronic myeloid leukaemia. British Journal of Haematology 2003, 121, 419-27.

21. Yehuda, O., Abeliovich, D., Ben-Neriah,S., Sverdlin, I., Cohen, R., Varadi, G., Orr, R., Ashkenazi, Y.J., Heyd, J., Lugassy, G. & Ben Yehuda, D. Clinical implications of fluorescence in situ hybridizations analysis in 13 chronic myeloid leukemia cases: Ph-negative and variant Ph-positive. Cancer Genetics and Cytogenetics. 1999; 114: 100-7.

22. M .M. T.el-Zimaity, H, Kantarjian, M. Talpaz et al.,'Results of imatinib mesylate therapy in chronic myelogenous leukemia with variant Phildelphia chromosome''British Journal of Haematology. 2004;vol 25: no2, 187-195.

23. G.Marzocchi,E Castagnetti and SLuatti. Vriant phildelphia translocations : molecular-cytogenetic characterisation and prognostic influence on frontline imatinib therapy, a GIMEMA Working Party on CML analysis''. Blood; 2011:vol117,no25,6793-800.

24. Masahiro Manabe, Yumi Yoshii, Satoru Mukai, Erina Sakamoto, Hiroshi Kanashima, Takeshi Inoue, and Hirofumi Teshima. A Rare t(9;22;16) (q34;q11;q24) Translocation in Chronic Myeloid Leukemia for Which Imatinib Mesylate Was Effective: A Case Report. Leukemia Research and Treatment Volume 2011; Article ID 592519, 3 pages doi: 10.4061/2011/592519.

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