CHROMOSOME ABNORMALITIES IN LEUKEMIA: A REVIEW

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SUMMARY

The common chromosome abnormalities that are encountered in the various types of leukemia are discussed here. Chromosome abnormalities in leukemia are non-random and certain chromosomal changes are now becoming recognised as being rather specific for certain leukemia types.

INTRODUCTION

It was in 1956 that doubts regarding the number of chromosomes in human cells were resolved. Tjio and Levan[1] found the number of chromosomes to be 46 after culturing cells from fetal lung tissue. Subsequently, with improvement in chromosome techniques and the development of banding techniques[2,3,4] it was possible to identify each chromosome exactly (Fig.1).

Cytogenetic studies in human leukemia are usually done on bone marrow cells by the direct method. Peripheral blood cells, splenic tissues and lymph nodes may also be used for cytogenetic studies. Tissues like the spleen and lymph nodes which usually contain dividing cells can be analysed by the direct method. Peripheral blood lymphocytes have to be subjected to *in vitro* culture and stimulated with mitogens such as phytohaemagglutinin in order to obtain dividing cells for chromosome analysis. This is the standard method employed in karyotyping an individual. In leukemias where the peripheral blood have a significant quantity of blast cells such as in blastic phase of chronic myeloid leukemia, mitogens need not be used because this may lead to a preponderance of normal diploid lymphocytes.

The disadvantage of the direct method is that in some cases of leukemia, few metaphase-stage cells may be available for chromosome analysis. But the direct method is still the method of choice in leukemias because it reveals a true karyotypic picture of the *in vivo* situation. Short term culture of marrow cells (12 to 24–hour culture) without the addition of mitogens can be used to increase the mitotic yield. This method may not give a true karyotypic picture of the *in vivo* situation because a different cell population may be at an advantage relative to the malignant clone.

Another problem encountered is that chromosomes of leukemic cells may be overcontracted, fuzzy and poorly banded while the adjacent normal cells may be of good quality. In such a situation, if one selects cells of good quality, the abnormal cells may not be adequately represented in the analysis.

The cell synchronisation technique introduced by Yunis[5] provides a much higher yield of chromo-

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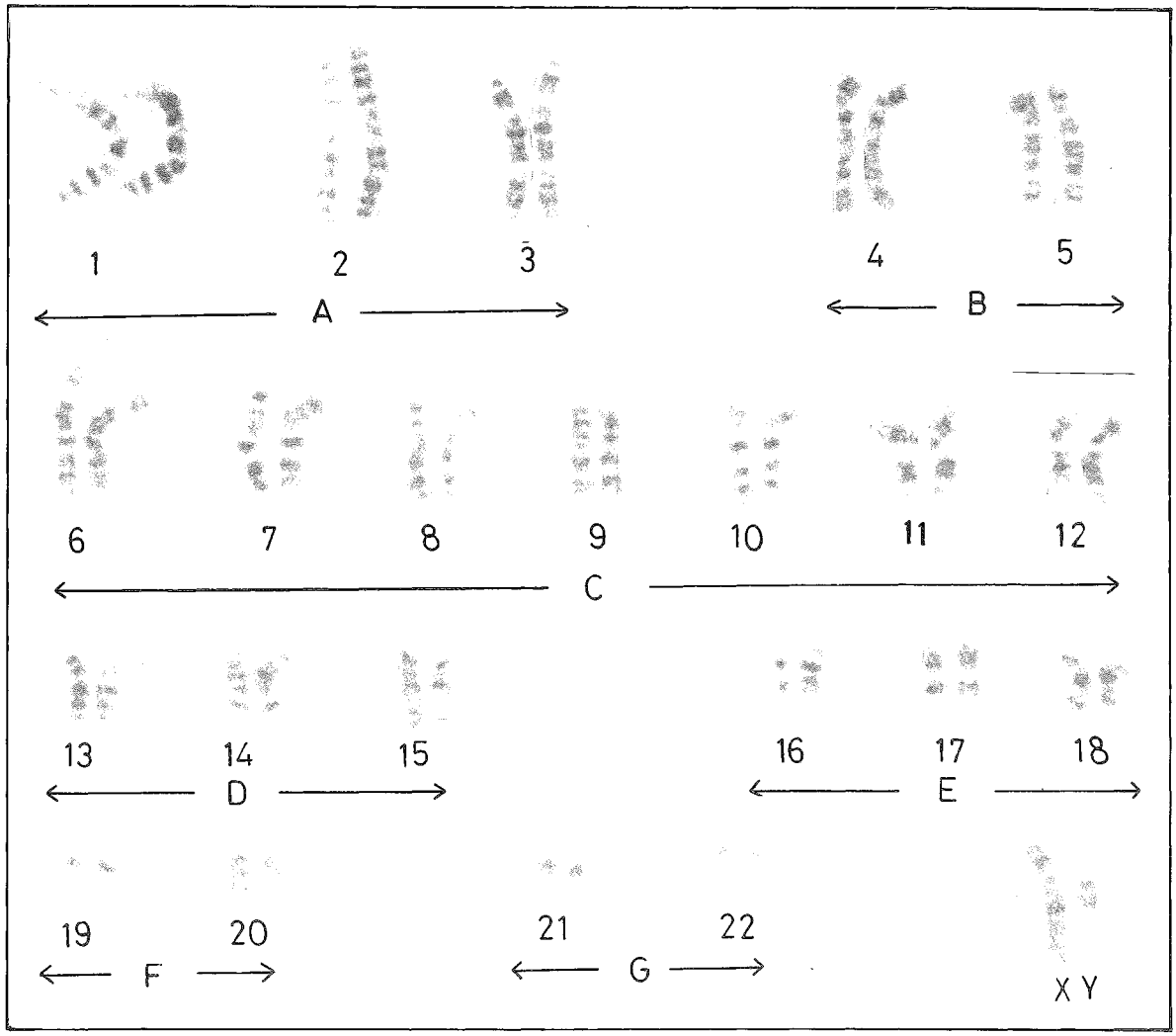

Fig. 1 Normal male karyotype. 2n = 46, XY. The chromosomes are Trypsin-Giemsa banded and arranged in groups according to decreasing size of chromosomes and position of centromere.

somal abnormalities in the acute non-lymphocytic leukemias.[6] This method is not at the moment commonly employed in most laboratories for the study of leukemia. Most reports on chromosomal changes in leukemia relate to findings using the direct method. This review, for practical reasons, has not included findings using the cell synchronisation method.

The banding techniques commonly used are Giemsa banding and Quinacrine banding. Reverse banding and Centromere banding are less commonly employed in leukemia work.

CHROMOSOME ABNORMALITIES IN LEUKEMIA: WHAT DO THEY MEAN?

There are three ways of associating a chromosomal abnormality and leukaemia—the chromosome change may cause the leukemia or the leukemia may cause the chromosome abnormality or the same factor which causes the leukemia also causes the chromosome abnormality seen.

It is not possible to conclude which of these possible associations might apply for any of the abnormalities observed to-date. However their

presence is more than of academic interest to the geneticist. The clinician is beginning to find usefulness in knowing the chromosomal pattern of the marrow cells in leukemia and other haematologic diseases. Hence this investigation now has a place in the clinical management of patients with these haematologic disorders.

In this paper, chromosomal abnormalities in leukemia will be reviewed under the following headings: Preleukemia, Chronic leukemia, Acute leukemia.

Preleukemia

Preleukemia generally occurs in elderly persons. A high proportion of these patients terminate in acute non-lymphoblastic leukemia (ANLL).

About 50% of preleukemic patients have an abnormal karyotype and in these patients the prognosis is poor with a fatal outcome of 60% compared with only 30% of patients with a normal karyotype.[7] The common chromosome abnormalities are an extra chromosome No. 8, a missing chromosome No. 7 or No. 5, and a partial deletion of the long arm of chromosome No. 7 or No. 5 (Fig. 2).[7]

Chronic Leukemia

Chronic lymphocytic eukemia (CLL) is commonly found in the western world but rare in the Orient. It is rarely seen in people below 30 years and is more common in males than in females.

The proliferating cells in over 95% of patients with CLL are B-lymphocytes. With the discovery of polyclonal B-cell mitogen such as lipopolysaccharide from *E. coli*[8,9] and Epstein-Barr virus [10,11] to stimulate the B-lymphocytes to undergo blast trans-

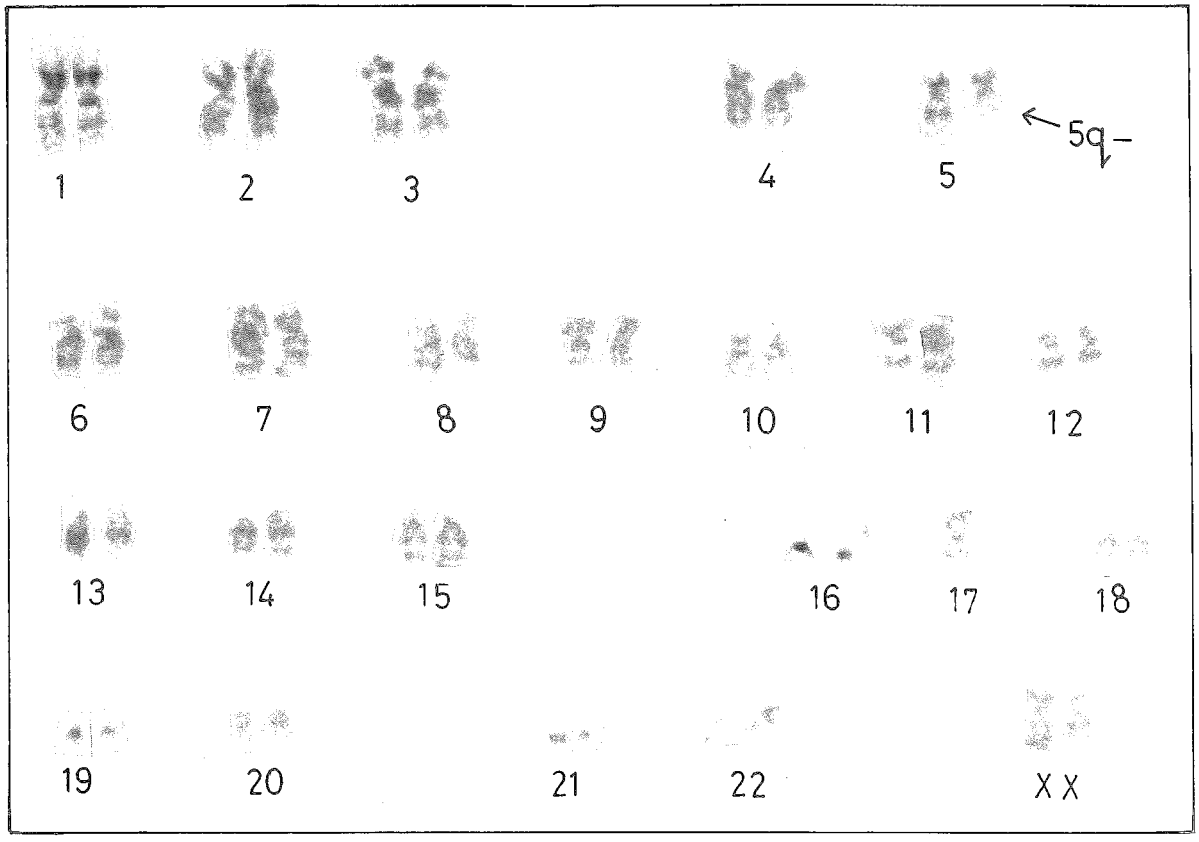

Fig. 2 Trypsin-Giemsa banded karyotype of a bone marrow cell from a female suffering from preleukemia. The arrow indicates a deletion in the long arm of chromosome No. 5. 2n = 46, XX, 5q−.

formation, cytogenetic analysis has been possible in B-cell CLL patients.

The incidence of an extra chromosome No. 12 in B-cell CLL is high[12,13] and its presence might signify a poorer prognosis.[14]

Several reports on findings in T-cell lymphoproliferative disorders have appeared[15,16,17] but these conditions are rare and will not be considered here.

The majority of the cases of chronic myeloid leukemia (CML), about 85% – 90%,[18] are characterised by the presence of a characteristic marker chromosome called the Philadelphia chromosome (abbreviated to Ph') in which the distal part of the long arm of chromosome No. 22 appears to be deleted (Fig. 3). This 'deleted' chromosome No. 22 is so called in honour of its city of discovery. Rowley[19] has shown that the Ph' chromosome originates from a translocation rather than a deletion.

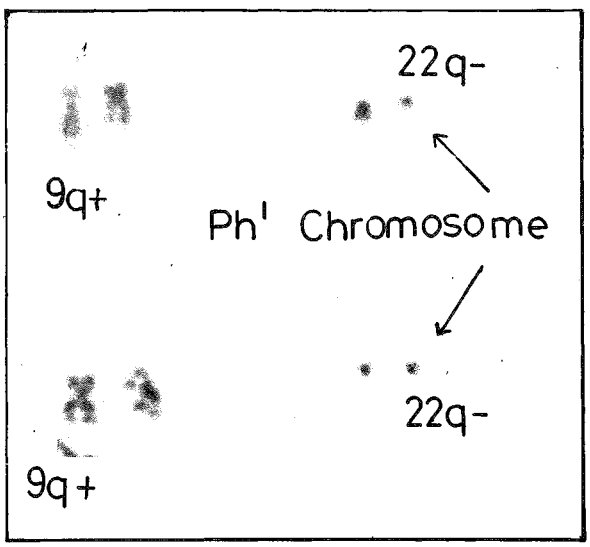

Fig. 3 Trypsin-Giemsa banded partial karyotype from two metaphases obtained from a patient with Philadelphia positive chronic granulocytic leukemia. There is translocation of material from chromosome No. 22 to No. 9, t (9q+; 22q–). The 'deleted' chromosome No. 22 *i.e.* 22q– is known as the Philadelphia (Ph') chromosome. The chromosome beside the 9q+ chromosome is the normal chromosome No. 9 and the normal chromosome No. 22 is beside the 22q– chromosome.

About 90% of the Ph' chromosome in CML is due to the standard translocation[20] probably balanced, between chromosomes No. 9 and No. 22, *i.e.*, t(9; 22) (q 34;q 11)*while 10% of the Ph' chromosome is due to variant translocation (so called "non-standard" Ph' chromosome). There are two types of variant translocations: one is a simple translocation in which the deleted part of chromosome No. 22 is apparently translocated onto a chromosome other than chromosome No. 9, and the other is a complex translocation involving three or more different chromosomes.

The survival of patients with CML having variant translocation, either simple or complex, was found not to differ significantly from that of patients with the standard Ph' translocation.[21] In another study,[22] it was found that the duration of the benign phase was significantly shorter for the non-standard Ph' patients (median 20 months) than for those with the standard Ph' (median 43 months).

The presence of Ph' – negative cells together with Ph'– positive cells in CML patients is not associated with any survival advantage.[23,24]

Studies have indicated that the Ph' chromosome in CML is clonal in origin. In females with CML who are heterozygous for an X-linked gene such as glucose-6-phosphate dehydrogenase all the cells involved in the leukemic process are of one polymorphic type.[25,26] Chromosomal polymorphism is either maternal or paternal in origin, but never both in the same patient.[27,28]

The Ph' chromosome is not only found in the myeloid cells but also the erythroid cells, megakaryocytes, monocytes[26,29] B-lymphocytes[30] and T-lymphocytes,[31] thus indicating that CML is a disease of the marrow stem cell.

*Translocation is the transfer of one or more chromosomal segments between chromosomes following breakage, e.g. t (9; 22). Translocation has occurred between chromosome No. 9 and No. 22. When the particular bands involved in the translocation have been identified the translocation may be described more accurately, e.g. t (9; 22) (q34; q11). The letters p and q are used to designate the short and long arms, respectively, of the metaphase chromosome. Bands are numbered from the centromere outwards.

The Ph' chromosome when present can be found in the bone marrow even during remission but not in the peripheral blood. It is present in the peripheral blood in untreated cases and during relapse only.

During the chronic phase of CML, chromosome abnormalities in addition to the Ph' chromosome are found in about 30% of CML patients.[28, 32, 33] The common chromosome abnormalities are: the presence of an extra chromosome No. 8 (Trisomy 8); isochromosome* for the long arm of chromosome No. 17; duplication or even triplication of the Ph' chromosome, and the loss of the Y chromosome in males.

When patients enter the terminal acute phase, about 20% will have only the Ph' chromosome while 80% will have additional chromosomal abnormalities together with the Ph' chromosome.[34, 35] The additional chromosomal abnormalities commonly seen in the acute phase of CML are almost similar to that in the chronic phase of CML.

About 10 – 15% of CML patients do not have the Ph' chromosome. They belong to a higher median age group and are mostly males. Ph'–negative patients appear to have a shorter life expectancy than Ph' –positive patients and they show a poor response to chemotherapy. The chromosome abnormalities seen in Ph' – negative CML patients most commonly involve the C group chromosomes.[36]

*An isochromosome is a metacentric chromosome *(i.e.* one the centromere is centrally placed) composed of duplicated short or long arms due to a transverse, rather than the usual longitudinal separation of the chromosome at the centromere.

**The '+' sign indicates an additional chromosome or chromosome material. If placed before the chromosome number it indicates an extra whole chromosome. When placed after the chromosome and its arm designation, it indicates an increase in the length of the particular chromosome arm. The '–' sign indicates a missing chromosome or chromosome material. If placed before the chromosome number it indicates a missing whole chromosome. When placed after the chromosome and its arm designation it indicates a decrease in length of the particular chromosome arm.

t (4q–; 11q+) indicates translocation between the long arms of chromosomes No. 4 and No. 11, with material being transferred from chromosome 4 to chromosome 11.

Acute Leukemias

The Ph' chromosome is not only found in patients suffering from CML. It occurs with an incidence of 25% in adults with acute lymphoblastic leukemia (ALL)[37, 38] and 2% in childhood ALL.[39] In patients with acute myeloid leukemia, the incidence is about 2 – 3%.[37, 40]

Only about 50% of Ph' – positive ALL patients achieve a complete remission. During complete remission the Ph' chromosome is absent in the bone marrow cells unlike in Ph'– positive CML. Some of these patients who achieve a complete remission may revert to the chronic-phase CGL where the Ph' chromosome reappears.

Thus Ph'– positive ALL has a lower remission rate; overall they have a worse prognosis compared to their Ph' –negative counterparts.

About 50% of patients with ALL have a chromosome abnormality. Besides the Ph' chromosome, other types of chromosome abnormalities commonly seen in ALL are:[41] t (4q–; 11q+) **especially in non-T, non-B ALL; 6q– found in non-B, non-T and T-cell ALL; 14q+ in B-cell and non-T, non-B ALL.

In childhood ALL, it was found that those cases with a hyperdiploid karyotype (more than 46 chromosomes) had a better prognosis compared to those with a normal karyotype. Those with a pseudodiploid karyotype (46 chromosomes with rearrangement of material within one or more chromosomes), however, had a poorer prognosis when compared to those with a normal and hyperdiploid karyotype. [42, 43] Pseudodiploidy is more common in males and in children less than two-years or more than 11 years. [43]

About 50% of cases of acute non-lymphoblastic leukemia (ANLL) have bone marrow cells with an abnormal karyotype.[40,44] These chromosome abnormalities reappear in relapse, sometimes with further chromosome changes. The cell population may be totally abnormal or there may be a mixture of chromosomally normal and abnormal cells. In general,

ANLL patients with totally abnormal chromosomes in the bone marrow have a poorer prognosis, to those with normal bone marrow chromosomes only.[40,45]

The common chromosome abnormalities encountered in ANLL are almost similar to those seen in preleukemia. In *de novo* ANLL, an extra chromosome No. 8 is the most common finding occuring with a frequency of 25% whereas −7 or 7q− and −5 or 5q− occur with a frequency of 14% and 8% respectively.[46] Abnormalities involving chromosomes No. 5 and No. 7 have been found commonly in ANLL patients secondary to treatment for a previous malignancy[47,48] or following occupational exposure to potential mutagenic or carcinogenic agents.[49]

Kaneko and colleagues[50] in their review have indicated that rearrangements involving the long arm of chromosome No. 11 were frequently seen in acute monocytic leukemia (45%) and acute myelomonocytic leukemia (11%).

Two significant structural changes are seen in ANLL − the translocation between chromosome No. 8 and No. 21, t (8; 21) (q22; q22)[51] in Acute Myeloblastic Leukemia (AML) of the M_2 type in French American British classification[52] and the translocation between No. 15 and No. 17, t (15;17) (q25 or 26; q22?)[53] in Acute Promyelocytic Leukemia (APL) of the M_3 type.

About 7 − 10% of AML patients of the M_2 type have the t (8; 21). This translocation is usually associated with the loss of the Y chromosome in about one third of the males or the X chromosome in about one third of the females.[54] In general, ANLL patients with chromosomal abnormalities have a poor prognosis but patients with the t (8; 21) are an exception. Their median survival is almost similar to those with a normal karyotype.[40,55]

An uneven geographical distribution of the translocation is observed: 24% in Chicago, 30% in Japan and none in Paris.[54]

About 40% of APL patients have the t (15; 17).[53] A variant form of APL in which almost every leukemic cell in the peripheral blood has an irregular and monocytoid nucleus and the cytoplasm is either devoid of granules or contains only a few fine azurophilic granules has been identified.[56] The t (15; 17) has also been found in this M_3 variant type.[53,57] Since this M_3 variant can be easily misdiagnosed as monoblastic leukemia, the correct diagnosis of these patients is of clinical relevance so as to reduce the risk of disseminated intravascular coagulation with therapy. It is apparent that cytogenetic studies may aid both the clinician as well as the pathologist here.

Geographical differences in the frequency of this t (15; 17) is also observed: all the six patients in Chicago and eight out of 12 patients in France have this traslocation.[53] The significance of the geographical differences of the t (8; 22) and t (15;17) is at present unknown.

CONCLUSION

Chromosome abnormalities in leukemia are non-random and tend to cluster to a few specific chromosomes. Cytogenetic investigation may help the clinician in the early and correct diagnosis of the leukemia, the type of leukemia, the prediction of its prognosis and its response to therapy. It is also a useful tool for the study of abnormal haemopoiesis and leukemogenesis.

The presence of chromosomal abnormalities in a dysmyelopoeitic syndrome (preleukemia and similar disorders of haemopoeisis) gives a grave prognosis, and a leukemic transformation is likely to occur early. The presence of additional chromosomal changes over and above the Ph' anomaly in CGL may herald the acute phase. Certain chromosomal changes are now becoming recognised as being rather specific for certain leukemia types.

It is evident that cytogenetic studies have a place in the routine diagnosis and management of leukemia and it is likely that with more experience we shall be able to learn more of its usefulness.

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