ABNORMALITIES OF CHROMOSOME 11Q IN THREE CASES OF ACUTE MYELOID LEUKEMIA

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ABSTRACT

The haematological findings and case history of 3 patients with the association of acute myeloid leukemia and translocation involving the long arm of chromosome no. 11 are presented. The recipient chromosome for the translocated material from chromosome 11 differs in all the three cases being namely chromosomes 1, 10 and 17.

Keywords: Abnormalities, chromosome 11q, acute myeloid leukemia

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INTRODUCTION

A case of acute myeloid leukemia (AML) is diagnosed when blasts constitute more than 30% of all nucleated marrow cells but there are less than 50% erythroid precursors, except for erythroleukemia. In 1976, the French-American-British (FAB) group[1] classifies AMLs morphologically into 7 subtypes namely myeloblastic leukemias (M1-M2), promyelocytic leukemia (M3), myelomonocytic predominant AMLs (M4), monoblastic predominant AML (M5; monoblastic M5a and promonocytic M5b), erythroleukemia (M6) and megakaryoblastic leukemia (M7).

Recent developments in cytogenetic techniques and immunocytochemical characterization of leukemias have led to a reclassification of the AMLs into 10-subclasses based on karyotypic-morphologic association by the Second Morphologic, Immunologic and Cytogenetic (MIC) Cooperative Study Group in 1988[2]. It is estimated that two-thirds of the AML cases show chromosome changes, 60% of which can be accounted for by one of 20 characteristic chromosome aberrations. These karyotypic aberrations have definite diagnostic and prognostic implications.

Abnormalities of the long arm of chromosome 11 (11q) with breakpoints at band q23-24 are characteristic of a group AML with a predominant monocytic component. They are found in about 35% of acute monocytic leukemia (M5 particularly M5a)[3,4] and, to a lesser extent, myelomonocytic leukemia (M4)[5]. Overall, the frequency of this abnormality in AML patients with abnormal karyotypes (M5a, M5b, M4) approximates 6%[2].

In this article, we describe three cases of AML with translocation involving the long arm of chromosome 11 with breakpoints at band q23.

MATERIALS AND METHODS

Cytochemical Studies

Bone marrow smears were stained with Wright-Giemsa, periodic acid Schiff (PAS), myeloperoxidase (MPO), Sudan Black etc. Morphologic classification followed conventions of the FAB Cooperative Group[1].

Cytogenetic Studies

Bone marrow cells taken at diagnosis were processed using two incubation techniques: overnight incubation with colcemid (0.5 µg colcemid) and overnight incubation with exposure of cells to 0.5µg colcemid for 1/2 hour at the end of culture.

Chromosome abnormalities were classified according to the International System of Human Cytogenetic Nomenclature[6]. A clone (a population of cells derived from a single progenitor cell) was defined by the presence of at least 2 cells with the same extra chromosome or the same structural change, or at least 3 cells with the same missing chromosome.

CASE REPORTS

The three patients in this study were Malaysians and were first seen at the hospital concerned between December 1988 and December 1989. Case 1 was admitted to the University Hospital, Kuala Lumpur, cases 2 and 3 were admitted to the General Hospital, Kuala Lumpur. The detailed clinical data of these 3 patients are reported below.

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Case 1

The patient is a 5-year-old Chinese boy who was apparently well until 3 months before admission when he presented with intermittent abdominal pain, was lethargic and suffered loss of weight and appetite. He was pale and had developed gum hypertrophy for the past two weeks. There was no history of bleeding or easy bruisability. The patient first consulted a private practitioner and a full blood investigation indicated a hemoglobin level of 8.8 gm %. The child was then referred to the University Hospital for further management.

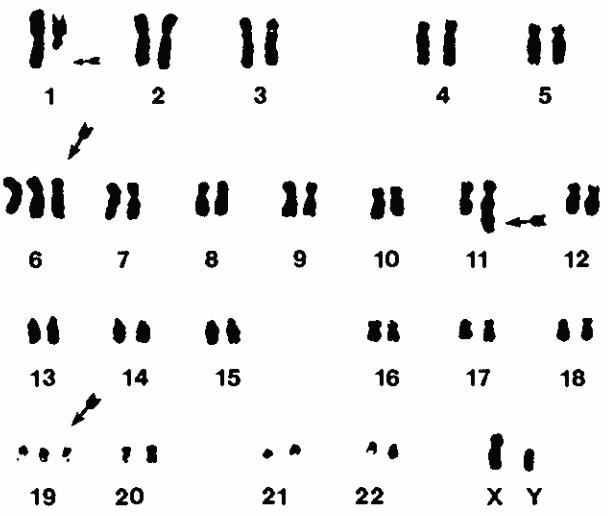
On examination, he was found to have diffuse swelling of the gums and generalized lymphadenopathy, inguinal and cervical. His abdomen was soft, non-tender, liver and spleen were not palpable. His white blood cell count (WBC) was 78,000/ul, haemoglobin 8.8 gm%, platelet count 136 x 10^3/ul, Na 136, K + 3.2, C1 97 mmol/1, creatinine 55 umol/1 and uric acid 273 umol/1. Bone marrow smear examination indicated marked hypercellularity with depression of normal hemopoiesis. Blasts constituted 90% of the nucleated cells, one pleomorphic with folded nuclei and moderate amount of cytoplasm. Cytochemical studies showed that more than 50% of the blast cells were positive for myeloperoxidase, and non-specific esterase. Some of the blasts displayed diffuse positivity to acid phosphatase but were negative to PAS. A diagnosis of acute myelomonocytic leukemia - M4 type - was thus made.

He was given blood and platelet transfusion. An induction chemotherapy consisting of cytosine arabinoside 100 mg/m^2 daily x 7, daunorubicin 20 mg/m^2 x 3, VP 16-213 150 mg/m^2 x 2, thioguanine 120 mg/m^2 / day x 4 and dexamethasone 5 mg/m^2/day x 4 was conducted and he responded well. He received 1800 rads of prophylactic cranial irradiation and completed consolidation chemotherapy. So far the patient remains in continued remission on maintenance Ara-C/thioguanine therapy. His parents rejected an autologous marrow transplant. Allogeneic bone marrow transplant is not feasiable because he is the only child.

Analysis of his bone marrow cell metaphases showed the following karyotype:

2n = 48, XY, t(1;11)(q21;q23), + 6, +19 (Fig 1).

Fig 1 - G-banded Karyotype from case 1. Arrows show the 1; 11 translocation, extra chromosome 6 and extra chromosome 19. 2n = 48 , XY, t (1; 11)(q21; q23), +6, +19



Case 2

A 31-year-old Malay man was first admitted to the General Hospital, Kuala Lumpur on 4 December 1988 with gum hypertrophy of one month duration, fever, loss of weight and appetite.

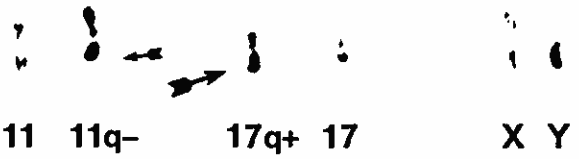
There was no history of bleeding tendencies or past medical history of significance. Physical examination revealed a pale and febrile patient who was jaundiced, with hepatosplenomegaly but no evidence of lymphadenopathy. Hematological data on admission showed a total white cell count of 56,500/ul, hemoglobin 8.6 g/dl and a platelet count 47,000. Differential count indicated a lymphocyte count of 25%, monocyte 4%, granulocyte 6%, blasts 53% and myelocytes 12%. Bone marrow examination showed an excess of blasts (>80%). Cytochemical and morphological findings were consistent with acute myeloid leukemia - M4 type.

The patient was started on chemotherapy consisting of adriamycin, cytosar and 6-thioguanine on the 8th day of admission. However the patient died on the same day from intracranial bleeding.

Cytogenetic studies indicated the presence of a translocation between chromosomes 11 and 17 as the sole chromosome change in 16 spreads:

2n = 46, XY, t(11;17)(q23;q25) (Fig 2).

Fig 2 - Partial Karyotype for case 2 showing the 11;17 translocation as the sole anomaly : 2n = 46, XY, t(11; 17)(q23; q25)



Case 3

A 2-year-old Indian girl presented with a month history of fever associated with weight loss. On examination, the patient was found to be pale and had enlarged liver and spleen. Peripheral blood showed a hemoglobin level of 5.4 g/dl, platelet count of 36 x 10^9/1, and white cell count of 5x10^9/1. The peripheral blood smear showed hypochromic microcytic anemia with neutropenia (2%) and 24% blasts. Her bone marrow was hypercellular composing of 85% blasts, 10% lymphocytes and 5% erythroid precursors. The blasts were large, some had fine granules and cytoplasmic vacuoles. Cytochemical studies indicated that the blasts were of the monocytic lineage. A diagnosis of acute myeloid leukemia - M5 type was made.

The patient discharged at own risk soon after and did not seek further treatment in the hospital. Hence no further details are available on her.

Cytogenetic studies showed the presence of a t(10;11) translocation as well as an extra chromosome 8 in all her marrow cells:

2n = 47, XX, t(10;11)(p13;q23), +8 (Fig 3).

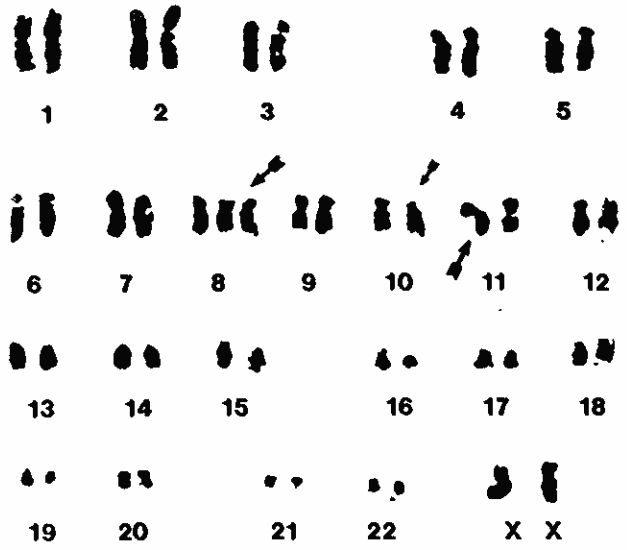
DISCUSSION

The most common translocation involving 11q appears to be with chromosome 9, t(9; 11) with the breakpoint in chromosome 9 ususally at p21-22[2].

Of the 3 translocations reported here, translocations between chromosomes 10 and 11 and that between chromosomes 11 and 17 are quite common found in AML, mostly with a

diagnosis of M5, and have also been observed in some cases of acute lymphoblastic leukemia (ALL)[7,8].

Fig 3 - G-banded Karyotype from case 3. Arrows show the 10; 11 translocation and the presence of an extra chromosome 8. 2n = 47, XX, t(10;11)(p13: q23), +8



A review of previously described cases of t(10;11) translocation by Kaneko et al[7] indicated that although the breakpoints are diverse, all were confined to the p13-p15 band of the short arm of chromosome 10, and either 11q13-14 or 11q22-q24 in the long arm of chromosome 11.

Of ten cases of t(11;17) translocation reviewed, although the break occurred mostly in 11q23-24, the breakpoint in chromosome 17 was variable, six cases had the break in 17q25, three in 17q21 and one in 17q23.

To our knowledge, 3 cases of AML-M4 with a t(1;11)(q21;q23) have been reported[9-11]. Our case is probably the fourth case reported since then and our findings further substantiate the view that the t(1;11)(q21;q23) may possibly delineate a new subtype within AML-M4.

Generally, leukemia with 11q23 involvement is characterised by a poor response to chemotherapy. However this prognostic implication is still premature as limited cases have been followed up and not for a reasonable length of time. The presence of other chromosomal changes, as observed in cases 1 and 3, could also have a bearing on the progress of the disease and its response to treatment.

Abnormalities of 11q are not only confined to AML but have been report in ALL, mostly of the T-cell type[2, 7, 12, 13]. Overall, 5.7% of childhood ALL cases were found to have these abnormalities[12]. Acute leukemias with 11q23 translocations are most frequently observed in congenital and infant leukemias[2] and generally are associated with a high leukocyte count[12]. Recent reports of biphenotypic features in the leukemic cells had led to the proposal that 11q-associated acute leukemias originate in a multipotent stem cell which could differentiate into both monocytic (myeloid) and/or lymphoid pathways[7,14].

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