

t(1;14) and trisomy 4 in a patient with concomitant leukaemias

Muhammad Nauman Zahir, Nehal Masood, Munira Shabbir-Moosajee

Abstract

Cytogenetic abnormalities have long been recognized as the genetic basis of the occurrence of various malignancies. Specific cytogenetic abnormalities have shown to occur recurrently in particular subtypes of leukaemias and lymphomas.

t(1;14) is an infrequently occurring recurrent chromosomal translocation that has been described in literature to be associated with haematological malignancies. Trisomy 4 is another rare genetic abnormality which has been reported in association with both acute myeloid and lymphoid leukaemias.

The concomitant occurrence of a myeloid malignancy in association with a lymphoproliferative disorder is a distinctly unusual phenomenon. We report the case of a young patient with concomitant T-cell acute lymphoblastic leukaemia and acute myeloid leukaemia with a novel cytogenetic abnormality i.e. t(1;14) with trisomy 4. We believe this is the first reported case where a patient with two concomitant haematological malignancies, harboured this karyotype.

Keywords: Chromosomal translocations, Acute myeloid leukaemia lymphoproliferative disorders, Trisomy, Karyotype.

Introduction

Cytogenetic abnormalities have long been recognized as the genetic basis of the occurrence of various malignancies. Chromosomal aberrations giving rise to neoplastic change predominantly comprise of chromosomal translocations, whole chromosomal gains (particularly trisomies) and aneuploidy.¹ All somatic cells can potentially exhibit recurrent chromosomal translocations. These mutations may arise de novo and may be either hereditary or acquired. Mutations may also be a complication of previous cancer therapy. Chromosomal translocations are the most common genetic defects that arise. The identification of these translocations has led to greater insight into the molecular characteristics of cancer cells and subsequently

has significantly increased understanding of the pathogenesis of cancer.

Leukaemias have historically been classified as per their morphological and immuno-phenotypical appearance. Extensive research has now highlighted that acquired clonal chromosome aberrations are found in a large proportion of malignant haematologic disorders. These mutations are proposed to be associated with malignant transformation, with specific cytogenetic abnormalities occurring recurrently in particular subtypes of leukaemias and lymphomas with some of them having prognostic significance.

The occurrence of a myeloid malignancy in association with a lymphoid disorder is a distinctly unusual phenomenon, especially in adults. The 8p11 myeloproliferative syndrome is one of these rare disorders in which patients usually present with concomitant or sequential development of a myeloid and lymphoid malignancy.²

We report the case of a young patient with concomitant T-cell acute lymphoblastic leukaemia (T-ALL) and acute myeloid leukaemia (AML) with a novel cytogenetic abnormality. We believe this is the first reported case where a patient with two concomitant haematological malignancies harboured this karyotype.

Case Report

A 27-year-old female was referred to our hospital with the history of generalized lymphadenopathy for 3 months. Lymphadenopathy had been progressive and was associated with odynophagia and dysphagia. The symptoms were accompanied with weight loss of 10kg over the past 3 months. On examination she had generalized lymphadenopathy with tonsillar enlargement.

Her baseline laboratory parameters demonstrated normochromic anaemia with anisocytosis and poikilocytosis. Her haemoglobin was 11.9gm/dl and she had leukocytosis (TLC count was $44.4 \times 10^9/L$) with 95% blast cells on peripheral film. Her platelet count, (was $205 \times 10^9/L$) creatinine, uric acid, electrolytes and liver function tests were all normal at the time. Serum lactate dehydrogenase was significantly elevated at 1084 IU/L

.....
Department of Oncology, Aga Khan University Hospital, Karachi.

Correspondence: Muhammad Nauman Zahir. Email: nauman.zahir@aku.edu

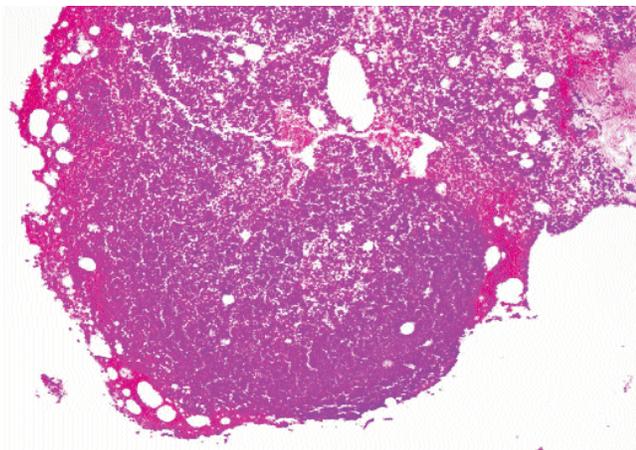


Figure-1: Diffuse infiltration of the marrow with myeloid blast cells.

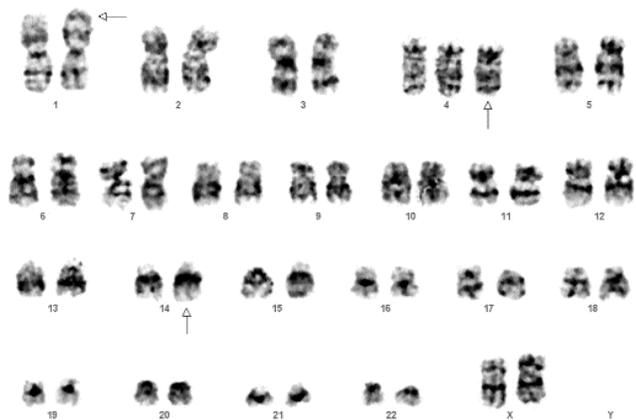


Figure-2: The karyotype of the patient showing t(1;14) and trisomy 4 [arrows].

(range 266-500 IU/L).

An excisional lymph node biopsy was performed which showed effacement of lymph node architecture by a lesion consisting of small/intermediate cells, with coarse chromatin and inconspicuous nucleoli showing brisk mitotic activity. This specimen stained positive for T-cell markers (CD 3, 5, 7 and 45) and was consistent with a diagnosis of precursor T-cell lymphoblastic lymphoma/leukaemia. A lymph node biopsy was done despite the presence of peripheral blasts to characterize the leukaemia better, to rule out dual pathology and as part of our institutional policy.

Bone marrow biopsy revealed a hypercellular bone marrow aspirate showing diffuse infiltration with blast cells. Some of these cells showed Auer rods. Normal haematopoiesis was suppressed although all three cell lines were seen. Bone marrow trephine biopsy showed

similar features (Figure-1) and 85-90% of blast cells stained positive with Sudan black. The blast cells were also strongly positive for MPO and TdT and showed patchy positivity for CD3.

Flowcytometry on the bone marrow aspirate demonstrated reactivity to myeloid markers i.e. cMPO, CD13, CD33 along with CD45 and CD34. The immunohistochemistry results from peripheral blood were similar to the bone marrow aspirate i.e. consistent with AML.

Flowcytometry on the bone marrow aspirate did not demonstrate reactivity to T cell markers. The T cell markers had stained positive on the excisional lymph node biopsy whereas bone marrow had demonstrated reactivity to myeloid markers thereby confirming the presence of concomitant haematological malignancies in this young patient.

A cytogenetic analysis of the marrow showed a complex karyotype -- 47,XX,t(1;14)(p34.1;q24),+4[12]/46,XX,t(1;14)(p34.1;q24)[3]/46,XX[10] [Figure-2]. 25 cells were counted — 12 harbouring 47 chromosomes and 13 showing 46 chromosomes. BCR/ABL was negative by fluorescent in situ hybridization (FISH).

It was then decided to treat her as AML and she was started on induction therapy with daunorubicin/cytarabine (3+7) (daunorubicin 90mg/m² on day 1-3 and cytarabine 100mg/m² as a 24 hour infusion on Day 1-7). She responded well to treatment with a quick resolution of the palpable adenopathy and clearance of blasts from peripheral blood by day 8 of induction therapy. On day 12 she began complaining of pleuritic chest pain, haemoptysis and fever. Chest X-Ray showed left sided lower zone infiltrates. Respiratory distress and haemodynamic compromise worsened over the next 12 hours and she had to be supported by mechanical ventilation. She was diagnosed with septic shock secondary to *Acinetobacter* species resulting from bilateral pneumonia. She progressively deteriorated over the next 3 days and died on day 16 of induction chemotherapy.

Discussion

t(1;14) is a very infrequently occurring recurrent chromosomal translocation and has been described to be associated with haematological malignancies. This cytogenetic abnormality is most commonly reported with lymphoid malignancies and the majority of the cases have reported its association with T-cell acute lymphoblastic leukaemia in children.³ There have been anecdotal cases in which it has been described in acute myeloid

leukaemia particularly AML-M0⁴ and bi-phenotypic leukaemia.⁵ *t(1;14)* is one of a number of distinct chromosomal translocations which have been identified and implicated in a proportion of T- ALL patients. The relatively commonly occurring *t(1;14)(p34;q11)* translocation observed in 3% of T- ALL results in the transposition of TAL1 proto-oncogene from its normal position on chromosome 1 into the T-cell receptor α/σ chain complex on chromosome 14. Additionally, some T- ALL patients have been identified with local rearrangements of the TAL1 locus that are not detectable by karyotype analysis. It has hence been postulated that inappropriate expression of TAL1 is the probable mechanism by which T- cell leukomogenesis is promoted by altered TAL1 alleles.⁶

Trisomy 4 is also a rare genetic abnormality. It can be seen in both acute myeloid⁷ and lymphoid leukaemias.⁸ In AML, it does not appear to have any prognostic significance unless it is also associated with kit mutations but appears to be a good prognostic marker in ALL.⁹

t(1;14), either as a sole abnormality or with another genetic mutation, has never been reported with a concomitant myeloid and lymphoid malignancy in literature. We believe that the patient described here is the first such case. Secondly, although the translocation *t(1;14)* has been described in association with haematologic malignancies in literature, the breakpoints described are different from the novel *t(1;14)* breakpoints of our patient. Our patient was found to have a *t(1;14)* along with trisomy 4 and we believe that this is the first such reported case.

The 8p11 myeloproliferative syndrome is another rare condition described in literature associated with concomitantly occurring leukaemias.² The presence of the characteristic translocation in both myeloid and lymphoid malignancies suggests involvement of a pluripotent stem cell. In theory then, the same should hold true for our patient where a novel cytogenetic abnormality affected a pluripotent stem cell, eventually giving rise to the

malignant bi-lineage differentiation. Unfortunately due to the non-availability of cytogenetic testing from the ALL component in our patient, we are unable to prove this hypothesis.

It is not clear as to whether the novel karyotype harboured by our patient was truly the cause for the development of her leukaemias. This is a question that can only be answered with further investigations. We believe however, that documentation of such novel cytogenetic abnormalities is of prime importance as they may serve to guide us towards the discovery of presently unknown mutations predisposing to the development of malignancy.

References

1. Mitelman F. Recurrent chromosome aberrations in cancer. *Mutat Res* 2000; 462: 247-53.
2. Goradia A, Bayerl M, Cornfield D. The 8p11 myeloproliferative syndrome: review of literature and an illustrative case report. *Int J Clin Exp Pathol* 2008; 1: 448-56.
3. Carroll AJ, Crist WM, Link MP, Amylon MD, Pullen DJ, Ragab AH, et al. The *t(1;14)(p34;q11)* is nonrandom and restricted to T-cell acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 1990; 76: 1220-4.
4. Tecimer C, Loy BA, Martin AW. Acute myeloblastic leukemia (M0) with an unusual chromosomal abnormality: translocation *(1;14)(p13;q32)*. *Cancer Genet Cytogenet* 1999; 111: 175-7.
5. Panani AD, Pappa V, Raptis SA. Novel constitutional translocations *t(3;5)(p25;q22)* and *t(1;14)(p31;q21)* in patients with acute leukemia. *Ann Hematol* 2004; 83: 156-9.
6. Bash RO, Crist WM, Shuster JJ, Link MP, Amylon M, Pullen J, et al. Clinical features and outcome of T-cell acute lymphoblastic leukemia in childhood with respect to alterations at the TAL1 locus: a Pediatric Oncology Group study. *Blood* 1993; 81: 2110-7.
7. Mecucci C, Van Orshoven A, Tricot G, Michaux JL, Delannoy A, Van den Berghe H. Trisomy 4 identifies a subset of acute nonlymphocytic leukemias. *Blood* 1986; 67: 1328-32.
8. Harris MB, Shuster JJ, Carroll A, Look AT, Borowitz MJ, Crist WM, et al. Trisomy of leukemic cell chromosomes 4 and 10 identifies children with B-progenitor cell acute lymphoblastic leukemia with a very low risk of treatment failure: a Pediatric Oncology Group study. *Blood* 1992; 79: 3316-24.
9. Beghini A, Ripamonti CB, Castorina P, Pezzetti L, Doneda L, Cairoli R, et al. Trisomy 4 leading to duplication of a mutated KIT allele in acute myeloid leukemia with mast cell involvement. *Cancer Genet Cytogenet* 2000; 119: 26-31.