

CASE REPORT

Double Philadelphia chromosome-positive B acute lymphoblastic leukaemia in an elderly patient

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Abstract

A rare case of double Philadelphia chromosome-positive B Acute lymphoblastic Leukaemia (B-ALL) is reported here. A 60-year-old lady presented with one month history of fever, submandibular lymphadenopathy, loss of appetite and weight loss. Physical examination revealed multiple palpable cervical lymph nodes. Blood film showed leucocytosis with 72% blasts. Bone marrow assessment confirmed a diagnosis of B-ALL with presence of double Philadelphia (Ph) chromosomes. As she was very ill, she was initially treated with an attenuated regimen of induction chemotherapy consisting of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) along with intrathecal chemotherapy comprising methotrexate, cytarabine and hydrocortisone. Bone marrow examination post-induction chemotherapy showed >5% blasts. She was subsequently re-induced with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) along with intrathecal chemotherapy, following which she went into complete remission. Consolidation chemotherapy consisting of methotrexate, methylprednisolone, cytarabine, intrathecal chemotherapy and imatinib was subsequently administered followed by maintenance chemotherapy consisting of vincristine, prednisolone and imatinib (IDEAMOP). She developed spontaneous bruises and relapsed four months into her maintenance chemotherapy with 90% blasts in the bone marrow which was treated with fludarabine, cytarabine and granulocyte colony stimulating factor (FLAG). Unfortunately she developed neutropenic sepsis which was complicated by invasive lung aspergillosis. Bone marrow examination post-FLAG showed 80% blasts. Despite aggressive antifungal therapy, her lung infection worsened and she finally succumbed to her illness 13 months after the initial diagnosis. We highlight a rare case of elderly B-ALL with double Ph chromosomes which carries a poor prognosis despite aggressive treatment for the disease and its complications.

Keywords: Double Philadelphia chromosomes, acute lymphoblastic leukaemia, imatinib, BCR/ABL

INTRODUCTION

Ph chromosome is present in 90-95% of chronic myeloid leukaemia (CML),¹ less often found in ALL and seldom present in acute myelogenous leukaemia.² Ph chromosome can be detected in about 25% of adult ALL and only 2-4% of paediatric ALL.¹ Although double Ph chromosomes have been reported in some cases of CML during blast crisis,³ it is very rare in ALL.² Ph chromosome-positive ALL is associated with a highly aggressive disease which is more resistant to chemotherapy when compared to

Ph chromosome-negative ALL⁴ and carries the worst prognosis amongst all the ALLs.¹ Current mainstay of treatment is a combination of tyrosine kinase inhibitor and intensive chemotherapy followed by allogeneic stem cell transplantation (SCT) after first remission.⁵ We report a rare case of an elderly lady with a diagnosis of double Ph chromosome-positive B-ALL who relapsed despite initial successful treatment with a combination of intensive chemotherapy and tyrosine kinase inhibitor.

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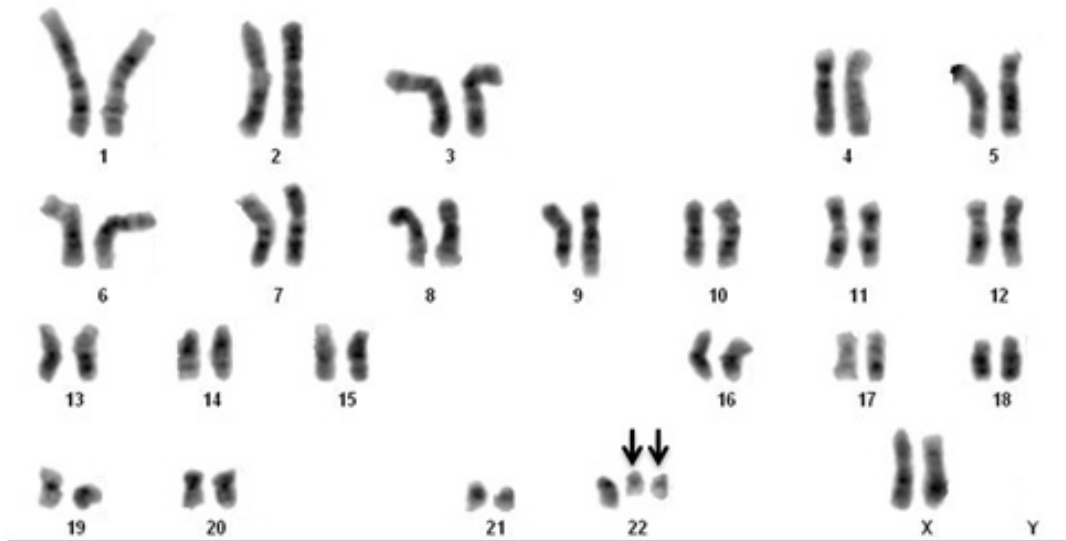


FIG. 1: Karyotyping of bone marrow showed 47,XX,t(9;22)(q34.1;q11.2),+der(22)t(9;22). There was presence of two truncated Ph chromosomes 22 (arrows).

CASE REPORT

A 60-year-old lady presented with a one month history of fever, submandibular lymphadenopathy, loss of appetite and weight loss. Physical examination revealed multiple palpable cervical lymph nodes but no evidence of organomegaly, bruises or petechiae. Full blood count (FBC) showed an elevated white cell count (WCC) of $144.6 \times 10^9/L$, mild anaemia with a haemoglobin (Hb) of 11.3g/dL and thrombocytopenia with a platelet count of $38 \times 10^9/L$. Blood film showed a leucoerythroblastic picture with 72% blasts. Bone marrow aspirate showed 70% blasts which were heterogenous in size with round to oval shaped nuclei, open chromatin pattern, inconspicuous nucleoli and minimal cytoplasm. The blast cells were negative for peroxidase stain. Immunophenotype of the blast cells showed positive expression for CD34, HLA-DR, CD19, cyCD79a, CD20, CD10, intCD22 and CD33. Bone marrow trephine biopsy was hypercellular and diffusely effaced by neoplastic lymphoid cells which have high nuclear cytoplasmic ratio with large round nuclei and prominent nucleoli. The cells were positive for TdT and CD79a but negative for CD3. These findings were consistent with B-ALL.

Bone marrow karyotype showed three metaphase with 47,XX,t(9;22)(q34.1;q11.2),+der(22)t(9;22) (Figure 1). FISH analysis of the bone marrow for BCR/ABL fusion using Abbott Molecular Vysis BCR/ABL dual colour, dual fusion translocation probe

has detected 87.5% of BCR/ABL fusion, with 52.5% of them harbouring three fusion signals, indicating the presence two Ph chromosome and one derivative chromosome 9 (Figure 2). The remaining 35% of the cells showed two BCR/ABL fusion signals, indicating the presence of one Ph chromosome and one derivative chromosome 9. Molecular genetic analysis by PCR showed presence of e1a2 BCR/ABL

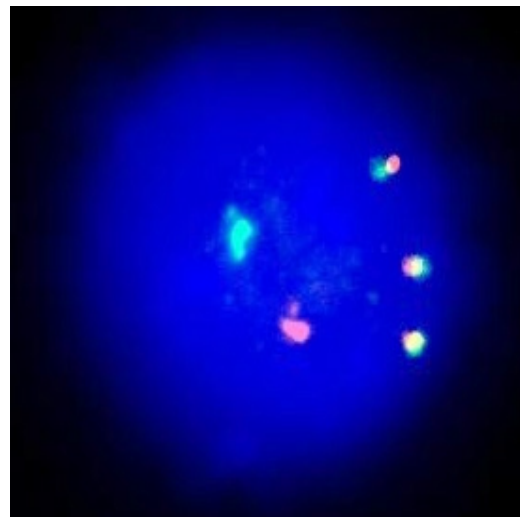


FIG. 2: FISH analysis of bone marrow for BCR/ABL fusion showed one green signal (normal ABL), one orange signal (normal BCR) and three fusion green/orange signals resulted from one derivative chromosome 9 and two truncated Ph chromosomes 22.

transcripts which encode for p190 kDa fusion proteins. Taking into account the cytogenetics findings, her final diagnosis was B-ALL with double Ph chromosomes.

Clinical course

As she was very unwell, she was initially treated with an attenuated regimen of induction chemotherapy consisting of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) along with intrathecal chemotherapy comprising methotrexate, cytarabine and hydrocortisone for central nervous system prophylaxis. Unfortunately bone marrow aspirate post induction chemotherapy showed >5% blasts. Subsequently she was re-induced with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) along with intrathecal chemotherapy. Bone marrow assessment post chemotherapy showed no excess of blast consistent with complete remission. Both FISH and PCR analysis post chemotherapy showed no BCR/ABL fusion. As she was ineligible for an allogeneic stem cell transplant, consolidation chemotherapy consisting of methotrexate, methylprednisolone, cytarabine, intrathecal chemotherapy and imatinib (IDEAMOP) was subsequently administered. She remained in complete remission after consolidation chemotherapy and subsequently received maintenance chemotherapy consisting of monthly courses of vincristine and prednisolone in addition to daily imatinib.

Four months into her maintenance chemotherapy, she developed spontaneous bruising suggestive of a clinical relapse. FBC showed pancytopenia with Hb 10.5g/dL, WCC $8.5 \times 10^9/L$ and platelet $32 \times 10^9/L$. Blood film showed 14% blasts and bone marrow aspirate showed 90% blasts which expressed CD34, HLA-DR, CD19, cyCD79a, CD20, CD10, int CD22 and CD33. Bone marrow trephine biopsy revealed a huge population of blast cells which were positive for TdT and CD79a but negative for CD3. Karyotype showed 2 metaphases with 47,XX,t(9;22)(q34.1;q11.2),+der(22)t(9;22) and FISH showed 15% BCR-ABL fusion. PCR analysis also revealed presence of e1a2 BCR/ABL transcripts. These findings were therefore consistent with relapse of her disease.

She was treated with an intensive chemotherapy regimen consisting of fludarabine, high-dose cytarabine and granulocyte colony stimulating factor (FLAG). During treatment, she developed neutropenic sepsis which was complicated

by invasive aspergillosis in the lungs. Bone marrow examination post-FLAG showed 80% blasts consistent with refractory disease. She was treated with intravenous amphotericin which was later switched to oral voriconazole. Unfortunately her lung infection worsened despite aggressive antifungal therapy. The patient eventually succumbed to her illness and died 13 months after the initial diagnosis.

DISCUSSION

Ph chromosome-positive ALL is found in 20-30% of adult cases and less than 5% of paediatric cases.¹ The incidence increases with age, approaching 50% in elderly patients greater than 50 years old.⁶ Clinically, patients with Ph chromosome-positive B-ALL present similarly when compared to other patients with B-ALL.¹ Patients usually present with signs and symptoms related to bone marrow failure such as bleeding, anaemia and infection. Ph chromosome-positive B ALL is a highly aggressive disease. It is usually more resistant to chemotherapy⁴ and associated with a shorter survival when compared to Ph chromosome-negative B-ALL.⁷ The principles of diagnosis are similar to ALL, relying on morphology and immunophenotyping by flow cytometry or immunohistochemistry in bone marrow trephine sections. Immunophenotyping usually displays surface expression of CD19, CD10, CD34, intTdT and frequent aberrant expression of CD13 and CD33 myeloid markers.⁸ CD25 expression is frequently associated with Ph chromosome-positive B-ALL in adults.⁹ Very few cases of Ph chromosome-positive ALL have a T precursor phenotype.¹⁰ Cytogenetic and molecular markers are required to establish the diagnosis of Ph chromosome-positive B-ALL. The administration of imatinib in addition to induction and consolidation chemotherapy for Ph chromosome-positive B-ALL is the current standard therapy.⁵ Owing to the dismal outcome with chemotherapy, allogeneic SCT is considered to be the treatment of choice in adult Ph chromosome-positive B-ALL.⁵

Double Ph chromosome-positive B-ALL has been described in several case reports worldwide.^{2,11-13} The possible mechanism of trisomy 22 (double Ph chromosomes and one normal chromosome 22) is believed to be the result of non-disjunction occurring during mitosis in the Ph chromosome-positive B-ALL clone (Figure 3). There is an error in mitosis in which members of a pair of sister chromatids

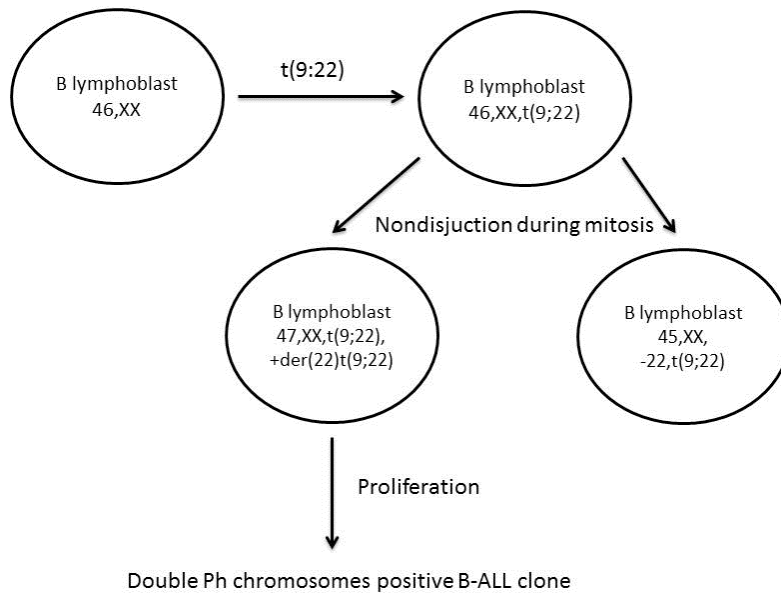


FIG. 3: Possible mechanism that could explain the generation of neoplastic clone with trisomy 22 (double Ph chromosomes and one normal chromosome 22)

chromosome 22 fail to separate properly from each other. In an earlier study conducted on 64 patients with relapsed or refractory Ph chromosome-positive ALL treated with imatinib, the percentage of double Ph chromosomes was reported to be as high as 36%.¹⁴ When compared to single Ph chromosome, double Ph chromosome-positive ALL patients were shown to have lower probability of complete haematological response (13% vs 39%; $p=0.04$), shorter time to progression (1.6 months vs 3.2 months; $p=0.006$) and inferior overall survival (5.2 months versus 9.6 months; $p=0.01$).¹⁴ 13 patients who had extra Ph chromosomes and/or BCR-ABL signals in greater than 20% of nuclei displayed a remarkably inferior time to progression (1 month) and overall survival (4.4 months).¹⁴ The primary cause of refractoriness to imatinib in Ph chromosome-positive ALL is due to the presence of extra Ph chromosome or BCR/ABL fusion gene.¹⁴ Reported cases of double Ph chromosome-positive B-ALL patients treated with different chemotherapy regimens such as hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine), APO (adriamycin, prednisone and vincristine) and VPLD (vincristine, prednisolone, L-asparaginase and daunorubicine) died due to either relapsed or refractory disease.^{2,12} Further large scale studies in the future are needed to determine the clinical significance and prognosis of double Ph chromosomes in B-ALL.

Conclusion

Ph chromosome-positive B-ALL is relatively common in elderly and those who express aberrant myeloid markers such as CD13, CD33 and CD25. Detection of BCR/ABL gene rearrangements is mandatory in B-ALL patients at diagnosis to determine the prognosis and choice of treatment because Ph chromosome-positive B-ALL confers a very poor prognosis which will require more aggressive treatment and consideration for allogenic SCT. The role of double Philadelphia chromosomes in B-ALL requires further large scale studies in order to provide further insight into the understanding and management of this subgroup which carries a very poor prognosis despite aggressive treatment with chemotherapy.

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