Early Lineage Switch from T-Acute Lymphoblastic Leukaemia to Common B-All

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ABSTRACT
Leukaemic stem cells have heterogenous differentiation potential. The immunophenotypes of blast cells are usually consistent throughout the disease course even at relapse. Rarely, blast cells may undergo a 'lineage switch' during the course of disease especially during relapse. We would like to highlight such a case in a 10-year old boy who presented with a two weeks history of lethargy, poor appetite, low...
grade fever, respiratory distress, cardiac failure, generalized oedema and hepatosplenomegaly. Full blood count showed a leucocyte count of $41.5 \times 10^9/L$ and platelet count of $37 \times 10^9/L$. The peripheral blood film showed presence of numerous blast cells. Bone marrow aspiration revealed a hypercellular marrow, which consisted of mainly blast cells with high nuclear to cytoplasmic ratio and inconspicuous nucleoli. Immunophenotyping and cytochemistry results were consistent with the diagnosis of T-cell acute lymphoblastic leukaemia. The patient achieved remission after treatment with UK ALL 97 protocol, regime B chemotherapy. However, he relapsed seven months after the initial diagnosis with 26% blast cells in the bone marrow aspirate. The majority was L1 blast cells admixed with some L2 blast cells. Immunophenotyping was consistent with common precursor B acute lymphoblastic leukaemia. The treatment was changed to a more lineage specific chemotherapy. Nonetheless, the patient never achieved remission and was planned for palliative management. This case illustrated a unique and rare case of rapid lineage switch from T-cell acute lymphoblastic leukaemia to common precursor B-cell acute lymphoblastic leukaemia.

Key words: early lineage switch, T-acute lymphoblastic leukaemia, B- acute lymphoblastic leukaemia

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is one of the common malignancies of the pediatric age group. It results from clonal proliferation of lymphoid precursors with arrested maturation. The disease can originate from lymphoid cells of B- or T-lineage, although mixed lineage leukemias do rarely occur. Its classification is based on morphological and cytochemical characteristics established by the French-American-British (FAB) group (Bennett et al. 1981). Today, the diagnosis of ALL is further facilitated by flow cytometry. Flow cytometric analysis allows for sub-classification of ALL by utilizing fluorochrome-labelled monoclonal antibodies. About 60% of ALL patients have early pre-B immunophenotype. The blast cells usually express CD 19, cytoplasmic CD 22, CD 79a, CD 10, terminal deoxynucleotidyl transferase (TdT) and 75% express CD 34. T-cell ALL accounts for 12-15% of ALL cases. The blast cells express surface CD 7, cytoplasmic CD 3, CD 2, CD 5 and TdT. The blast cells may also express aberrant antigens which do not belong to the main lineage. Immunological characterization of acute leukaemia is therefore essential in defining cell lineage to aid treatment options and determination of prognosis.

The lineage of the leukaemic blast usually remains similar throughout the disease course, although the pattern of antigen expressions may change slightly. However, a switch of lineage of blast cells does rarely occur. Pui et al. described cases which showed switch from lymphoid to myeloid phenotype or the reverse (Pui et al. 1986). From literature review, phenotypic lineage switch rarely occurs from T-ALL to B-ALL or vice versa and to the best of our knowledge, only one case has described this phenomenon (Besalduch et al. 1990). Our case illustrates an unusual phenotypic switch in leukaemic cells from a patient who first presented with T-cell acute lymphoblastic leukaemia who had gone into remission and relapsed seven months later with common pre-B ALL.
CASE REPORT

A 10-year-old boy presented with two weeks history of low grade fever, lethargy and poor appetite. The patient was the youngest of four siblings. His father, a 36-year-old man worked as a printing officer at a private company and his mother, a 36-year-old woman, was a housewife.

At presentation, the patient was pale and in respiratory distress. His blood pressure was 105/40 mmHg, pulse rate of 168 bpm and oxygen saturation was 100% under nasal prong oxygen. Physical examination revealed pleural effusion over the right lung and cardiomegaly. There were hepatosplenomegaly measuring 5 cm and 4 cm below the subcostal margins respectively.

Laboratory investigation results showed haemoglobin (Hb) 4.9 g/dL, total white blood cells (WBC) 41.5x10⁹/l, platelets 37x10⁹/l, neutrophils 0.8x10⁹/l, lymphocytes 38.6x10⁹/l. The peripheral blood smear showed presence of numerous blast cells. The blast cells exhibited high nuclear to cytoplasmic ratio with inconspicuous nucleoli (Figure 1).

His chest radiograph showed cardiomegaly with mediastinal widening. The bone marrow aspirate showed presence of more than 90% blast cells which were homogenous in size, showing high nuclear to cytoplasmic ratio with basophilic cytoplasm and inconspicuous nucleoli. Other cell lines were depressed. The blast cells were negative for peroxidase and periodic acid Schiff stains. These findings were consistent with acute lymphoblastic leukaemia, FAB-L1. The trephine biopsy showed similar findings. Flow cytometric analysis of the peripheral blood and bone marrow aspirate showed that the population was positive for T-cell markers; CD 2, intracellular CD 3, CD 4, CD 5, CD 7, CD 8, HLA-DR but negative for CD 19, CD 79a, CD 56, CD 117, intra MPO, CD 13 and CD 33 (Figure 2). Marrow cytogenetic study revealed a 46 XY normal karyotype with negative BCR-ABL translocation.

The patient achieved remission with UK ALL 97 protocol regime B induction chemotherapy. However, at week 20, his bone marrow aspirate revealed presence of excess blast cells of 10%. Flow cytometry analysis was inconclusive due to sample inadequacy. He subsequently received Doxorubicin, Vincristine, Dexamethasone and Asparaginase as per delayed intensification 1 chemotherapy protocol which was complicated by bronchopneumonia secondary to febrile neutropaenia. The repeat bone marrow examination at week 25 showed persistence of excess of blast cells (7%). The bone marrow examination was repeated at week 29 and showed presence of more than 26% blast cells which comprised of two populations of blast cells (Figure 3). One population was larger with abundant basophilic cytoplasm (morphologically L2 blast cells) while the other population was smaller, more homogenous with very scanty cytoplasm (L1 blast cells). The two populations of blast cells showed variable antigen expressions. Both populations of blast cells expressed CD 19, anti-HLA-DR, CD 10 and cytoplasmic CD 22. One population of blast cells was CD 34 positive with negative CD 20 while the other population was CD 34 negative with positive cytoplasmic CD 20. The blast cells were negative for intra CD 3, CD 7, CD 117, intra-MPO, CD 13 and CD 33 (Figure 4). A diagnosis of precursor B-cell acute lymphoblastic leukaemia with CD 10 positivity (CALLA) was then made and the patient was started on the German Relapse Protocol (GRP). Repeat bone marrow examination after four months of relapse showed excess of blast cells (10%). The blast cells were mostly large in size with relatively abundant cytoplasm. A second course of chemotherapy was given for eight days.
Figure 1: Peripheral blood film of the patient showed presence of numerous blast cells with high nuclear:cytoplasmic ratio and inconspicuous nucleoli (arrow). (Wright stain, x 200)

Figure 2: Flow cytometric analysis of the bone marrow sample showed a single population of blast cells (red) expressing CD 3, CD 7, CD 4 and CD8 but negative for CD 34 and B-markers.
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Figure 3: Bone marrow aspirate at relapse showed numerous blast cells. Some of the blast cells were large with relatively more cytoplasm (arrows) while the other blast cells were small with scanty cytoplasm (arrow heads). (MGG, x 400)

Figure 4: Flow cytometric analysis of the patient’s bone marrow aspirate showing two blast cell populations, one expressed CD 34 and negative for CD 20 surface markers (red population), while the other expressed CD 20 but negative for CD 34 yellow population. However, both blast cell populations expressed HLA-DR, CD 10, CD 19 (dot plot not shown) and cytoplasmic CD 22.

Review of bone marrow examination after completing two courses of chemotherapy showed persistence of blast cells (10% blast cells). In view of this condition, bone marrow transplant was no longer a therapeutic option. The management was then changed to palliative care which included low-dose chemotherapy and prophylactic treatment for infections.

DISCUSSION

Leukaemic stem cells have heterogenous differentiation potential. It has been well described in various articles that many different patterns of inappropriate expression of lineage markers were observed in acute leukaemias. The spectrum of mixed acute leukaemias includes biphenotypic leukaemia with markers of
more than one lineage of antigen expressions present on the same blast cells, bilineal leukaemia with two distinct populations, and biclonal leukaemia with two distinct leukaemic cells of independent origins (Hoffbrand et al. 1988). These terms have recently however been revised in the WHO classification 2008. The term mixed phenotypic acute leukaemia (MPAL) is now applied to both biphenotypic and bilineal leukaemia in general, with more specific terms B/myeloid (B/MY) and T/myeloid (T/MY) leukaemia which refer to leukaemias containing the lineages specified, irrespective of whether one or more than one population of blast cells is seen (Borowitz et al. 2008). There are cases of MPAL based on one criterion at diagnosis (e.g biphenotypic leukaemia) which change over time at relapse to the other (bilineal leukaemia), or vice versa. Furthermore, following therapy, persistent disease or relapse may occur as either pure ALL or AML. In some cases, this phenomenon has been termed ‘lineage switch’.

The phenotypes of blast cells from patients with ALL upon relapse most often adhere to the original lineage (Greaves et al. 1980). However, blast cells which undergo a ‘lineage switch’ during the course of disease especially during relapse had been estimated in some series to be as high as 8% (Stass et al. 1986). In this case, a phenotypic lineage switch is seen where the blast cells initially expressed T-cell markers (cytoCD3+, CD2+, CD4+, CD8+, CD5+, CD7+) at diagnosis. However at relapse, the blast cells were positive for B-cell markers (CD19+, intracD22 and CD20) and also showed positivity towards CD10, CD34, HLA-DR but negative for cytoplasmic CD3, CD7, CD117 and anti-MPO. The mechanism of lineage switch remains unclear. Most cases demonstrated consistent chromosomal findings at the time of diagnosis and switch and were therefore thought to be clonal in origin (Stass et al. 1984, Mantadakis et al. 2007). It was hypothesized that chemotherapy might have induced suppression of a clone apparent at diagnosis, allowing the expansion of another clone with different markers, which was resistant to treatment (Stass et al. 1984). Alternatively, the therapy might have a leukaemogenic effect on a normal hemopoietic cell and the lineage switch might then represent the induction of a new malignancy rather than transformation of the initial leukaemic cells. In support of this view, there were cases described with a complete variation of cytogenetic markers at diagnosis and relapse (Park et al. 2011) and after allogenic bone marrow transplantation (Brito-Babapulle et al. 1989). However, therapy-induced acute leukaemia had a long latency period of about 69 months as described in a large multicentre GIMEMA trial reported by Pagano et al. in 1998.

As in this case, there was a rapid lineage switch with an interval of just seven months from first presentation to relapse. As the time frame was too short, it was very unlikely for secondary malignancy to have set in. Thus, the most likely pathogenesis for the lineage switch in this case was chemotherapy-induced suppression of the apparent leukaemic clone at diagnosis, while allowing the expansion of another clone with different markers which was resistant to treatment. A similar conclusion was also reached by Shivarov et al. who reported a very early onset lineage switch from B-ALL to AML in an adult patient within a period of only 3 months after the initial diagnosis (Shivarov et al. 2009).

A variety of genetic anomalies has been reported in cases of ambiguous lineage leukaemias especially mixed phenotype acute leukaemia. The t(9;22)(q34;q11) BCR-ABL1 translocation and translocations associated with the MLL gene are the two most common genetic anomalies associated with MPAL.
In the case of lineage switch, the data are scanty, but two cases have been reported to involve t(9;22)(q34;q11) BCR-ABL1 translocation in two cases of Ph+ALL to Ph+AML (Pane et al. 1996, Reardon et al. 1994).

In a study of immunophenotypic and cytogenetic changes at relapse by Hur et al. in 2001, of 99 patients, 51 patients (51.5%) had immunophenotypic changes at relapse with expression of aberrant markers to be more frequent at relapse than at initial diagnosis especially in B lineage ALL (41.1% versus 10.3%). Cytogenetic changes at relapse were observed in 28 of 46 patients (60.8%). The initial abnormal karyotypes were more frequently associated with clonal changes at relapse compared to initially normal karyotypes (78% versus 43%) (Hur et al. 2001).

Loss of CD10 and other antigens at relapse has been reported in about 15% of ALL patients, however a complete change of phenotype from T-cell ALL to B-cell ALL is rare. From literature search, only one case in 1990 had the same phenomenon. Besalduch et al. in 1990 described a case of a 17-year old boy who first presented with massive hepatosplenomegaly and a mediastinal mass and was diagnosed to have T-cell acute lymphoblastic leukaemia. He was given standard chemotherapy and achieved remission. However, he relapsed 4 years later as precursor B-ALL.

In a study by Stass et al. in a series of 264 newly diagnosed acute leukaemia, of the 239 patients who attained complete remission, 89 relapsed with six cases (6.7%) demonstrating lineage switch from acute lymphoblastic leukaemia to acute myeloid leukaemia or vice versa. Of the six cases, four had T-cell associated characteristics either at diagnosis (three cases) or at lineage conversion (one case) suggesting that T lymphoblasts may have the potential for myeloid differentiation or that there may be a multipotential progenitor cell capable of both T lymphoblast and myeloblastic differentiation. Of 30 patients with T-ALL at diagnosis, 10 of the 89 patients who relapsed had T-cell ALL. Thus, 30% of T-ALL patients who relapsed demonstrated lineage switch. The issue is highlighted here to show the heterogeneity of T-lymphoblast differentiation which, in this case evolved to B-lymphoblast at lineage conversion. This study also indicated that lineage switch in acute leukaemia was more common than might have been expected, possibly because of the wider use of intensive chemotherapy.

More studies are needed to identify the target cells in leukaemogenesis to evaluate their spontaneous or drug induced capacity for lineage deviation and differentiation, and to elucidate the relationship between the genetic and phenotypic characteristics of leukaemic cell lineages.

Prompt recognition of lineage switch may be helpful in selecting an effective therapeutic regimen. Ultimately, therapy appropriate for the leukaemic phenotype at the time of lineage switch may be advisable.

**CONCLUSION**

Conversion of T-cell lineage ALL to B-cell lineage ALL is a rare occurrence. This case illustrated a phenotypic lineage switch from a characteristic T-ALL to common precursor B-ALL. In our case, lineage conversion occurred seven months after the initial diagnosis which was postulated to be likely due to chemotherapy which eradicated the dominant clone apparent at diagnosis, permitting expansion of a secondary clone with a different phenotype. Rapid recognition of this condition is needed to tailor treatment decision and strategy for disease monitoring.
REFERENCES


