

## B-Acute Lymphoblastic Leukemia in a Follow-up Case of Breast Cancer

Sir,

Therapy-related leukemias are a well-known complication of the treatment of solid or hematological malignancies. Among solid malignancies, breast cancer is the most common cause of therapy-related leukemias. Therapy-related leukemias usually present within 5–7 years of the primary treatment. The majority of these leukemias are of the myeloid lineage, but therapy-related acute lymphoblastic leukemia (t-ALL) has been rarely described. Because of the rarity, the clinical and molecular markers have been poorly described in t-ALL. Hence, we report a case of B-acute lymphoblastic leukemia (ALL) developing in a patient of carcinoma breast on follow-up.

### Case Report

We report a case of 40-year-old female, who was diagnosed with breast cancer, Stage IIIA (AJCC 7<sup>th</sup> edition) with a hormonal profile of ER+ (8/8)/PR+ (6/8)/Her2-. She received standard adjuvant chemotherapy with 4#FEC (5-fluorouracil - 600 mg/m<sup>2</sup>, epirubicin - 75 mg/m<sup>2</sup>, cyclophosphamide - 600 mg/m<sup>2</sup>) and 4#Docetaxel (85 mg/m<sup>2</sup>). After completion of chemotherapy, she underwent chest wall radiation 50 Gray/25#/5 weeks. Along with radiotherapy, she was started on hormone therapy with tamoxifen. She completed her radiotherapy in August 2014 and after which was on regular follow-up with annual gynecology examination and mammogram.

She presented to us at the end of September 2018 with complaints of easy fatigability and generalized weakness. On clinical examination, she was pale with multiple, bilateral, level 2–3 cervical lymph nodes with hepatosplenomegaly (liver-4 cm and spleen-6 cm below the costal margin).

On further evaluation, she had pancytopenia with suppression of all hematopoietic lineages. Her bone marrow aspiration repeatedly showed dry tap, and her bone marrow flow cytometry could not be done despite multiple attempts. However, bone her bone marrow biopsy showed large areas of fibrosis with immature cells (blasts) suggestive of B-ALL with CD20+, TDT+ [Figure 1]. With a final diagnosis of B-ALL, she was started on B-ALL (AYA) protocol with a further aim of HLA-Matched Allogenic Stem Cell Transplant. At present, she has completed the induction phase and her postinduction bone marrow examination is in complete remission.

### Discussion

Therapy-related leukemias are one of the known and rare complications of anticancer drugs. Out of myeloid and lymphoid series, most of the cases of secondary leukemia are reported to be acute myeloid leukemia/myelodysplastic syndromes. t-ALL are among one of the rare causes of ALL. The incidence of t-ALL is difficult to decipher as the results of larger studies have been confounded by the inclusion of secondary ALL (s-ALL) [Table 1]. In most of the studies, both t-ALL and s-ALL account for <1.5%–2.5% cases of ALL.<sup>[5,6]</sup>

Out of all anticancer drugs, alkylating agents and topoisomerase inhibitors are the most common drugs to be associated with therapy-related hematological malignancies. Therapy-related myeloid neoplasms have been reported to occur with a latency of 5–7 years with alkylating agents and 1–3 years with topoisomerase II inhibitors.<sup>[7]</sup>

In the recent study by Aldoss *et al.*,<sup>[1]</sup> the median time to develop t-ALL was 6.8 years. Breast cancer was the most common primary malignancy reported in their cohort. In

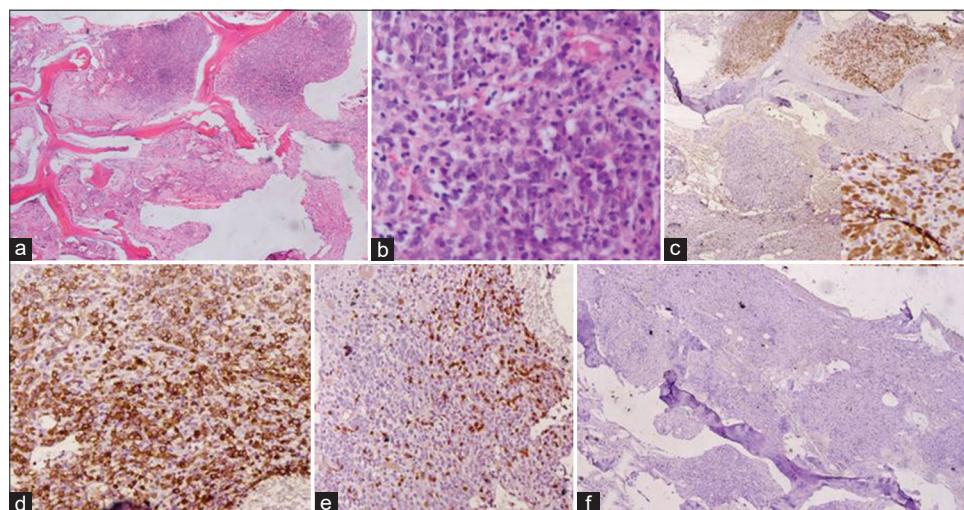


Figure 1: (a) Microphotograph shows bone marrow biopsy with large areas of fibrosis. (b) The well preserved space shows immature cells (blasts). The cell are immunopositive for TDT [(c) ×200], CD20 [(d) ×200] while negative for CD3 [(e) ×200] and MPO [(f) ×100]

**Table 1: Studies on therapy-related acute lymphoblastic leukemia (t-ALL) and secondary acute lymphoblastic leukemia (s-ALL)**

Author (year)	Sample size	Frequency (%)	Age (years)	Most common solid tumor	Interval to develop ALL (years)	Cytogenetic abnormality	OS (median)
Aldoss <i>et al.</i> , 2018 <sup>[1]</sup>	Total: 1022 93: t-ALL	9.1	55	Breast cancer (25%)	6.8	29: Ph 16: MLL 5: Complex	2 years OS: 66.2%
Rosenberg <i>et al.</i> , 2017 <sup>[2]</sup>	Total: 14,470 371 (3%): s-ALL and t-ALL	3	>70	Breast cancer (21%)	5.5	-	-
Abdulwahab <i>et al.</i> , 2012 <sup>[3]</sup>	23: t-ALL	6.9	51	Breast (40%)	4	8: MLL 4: BCR-ABL	13.6 years
Shivakumar <i>et al.</i> , 2008 <sup>[4]</sup>	101: t-ALL Age (years): <18: 29 18-59: 54 ≥60:18	-	-	Age (years): <18: Neuroblastoma 18-59: Hodgkin's disease ≥60: Breast and prostate cancers	Age (years): <18: 3 18-59: 2.2 ≥60: 1.8	Most common Age (years): <18: MLL 18-59: MLL ≥60: Normal	Age (years): <18: 0.6 18-59: 0.5 ≥60: 0.54

ALL – Acute lymphoblastic leukemia; OS – Overall survival; t-ALL – Therapy related ALL; s-ALL – Secondary ALL; Ph – Philadelphia; MLL – Mixed lineage leukemia; BCR-ABL – Breakpoint cluster region-Abelson

their retrospective cohort, 83% of the patients had available molecular markers, and the most common abnormality was Philadelphia (Ph) chromosome, followed by normal karyotype and mixed-lineage leukemia (MLL) gene rearrangement.

Our patient presented within 5 years of chemotherapy. She presented with typical symptoms of acute leukemia leading to symptoms of bone marrow failure. We could not identify any molecular abnormality of polymerase chain reaction and karyotyping studies because of the dry tap on bone marrow aspiration. This also raises a question of whether it was a therapy-related leukemia or an incidental finding of a breast cancer patient developing leukemia on follow up.

Therapy-related leukemias are biologically different from *de novo* ALL in terms of the clinical and molecular findings. The most consistent finding which has been reported among various series is the presence of molecular markers.<sup>[4,8]</sup> The most consistent and common molecular markers associated with t-ALL are the presence of Ph chromosome and MLL gene rearrangement [Table 1].

It is difficult to arrive at a firm conclusion regarding the prognosis of patients with t-ALL because of the rarity of cases, but previous studies have reported t-ALL has a poor prognosis. Because of rarity, clinicians struggle to define a standard leukemia protocol, and the role of stem cell transplant has not been defined clearly.

According to the literature, data are sparse regarding ALL occurring as a therapy-related leukemia in a follow-up case of breast cancer. We could find only one case series of five patients published from India.<sup>[9]</sup> In which of five patients, only one had t-ALL. Hence, we report this case to increase the awareness of the same and the need for a high index

of suspicion and the importance of regular follow-up even after remission of the primary malignancy.

The large scale database search is required to know the exact incidence and the outcomes of patients with t-ALL in Indian patients.

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#### Conflicts of interest

There are no conflicts of interest.

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