

Case Report

## Chemotherapy causes cancer! A case report of therapy related acute myeloid leukaemia in early stage breast cancer.

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### ABSTRACT

Use of chemotherapy and radiotherapy in the adjuvant setting has improved survival for many patients with malignancy. Unfortunately multimodality treatment can come at a price, in particular therapy-related malignancies. This has importance in that patients must be made aware of this potential detriment from therapy and doctors must consider this diagnosis in those patients who are cancer survivors and presenting with health problems. We present a case report and brief overview of the literature regarding chemotherapy-induced acute myeloid leukaemia (AML) following therapy for early stage breast cancer.

**Keywords:** therapy-related leukaemia, breast cancer, adjuvant chemotherapy.

A 52 year old woman had a mastectomy and axillary node clearance for a T2 NO MO infiltrating ductal carcinoma of the left breast which was grade 2 and hormone receptor positive. Past medical history included ulcerative colitis, she was taking no regular medications. Subsequently she received 4 cycles of adjuvant chemotherapy consisting of doxorubicin (60mg/m<sup>2</sup>) and cyclophosphamide (600mg/m<sup>2</sup>), followed by a 5 week course of radiotherapy and 5 years of tamoxifen. Six years following her surgery she was referred to the haematology clinic with thrombocytopenia, (Platelet count = 60x10<sup>9</sup>/L (150-400)). This coincided with the introduction of mesalazine for a flare up of her normally quiescent colitis.

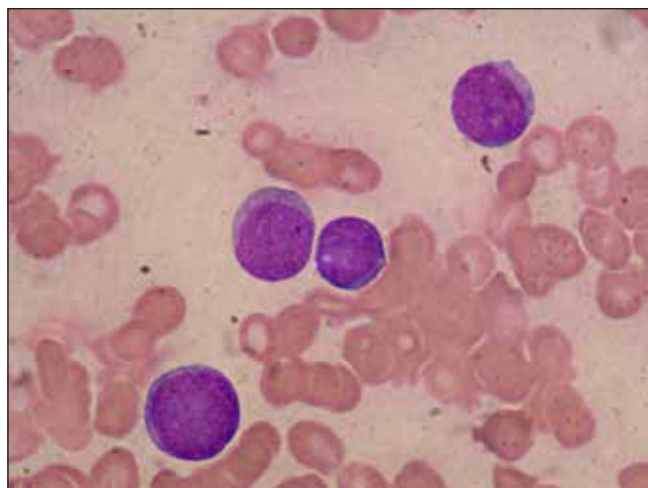


Fig 1. Peripheral blood film showing multiple myeloblasts.

An initial bone marrow biopsy was inconclusive and a presumptive diagnosis of either Idiopathic Thrombocytopenic Purpura (ITP) or drug-induced thrombocytopenia (DIT) was made. She was reviewed 6 months later by which time her

platelet count was 30x10<sup>9</sup>/L. She was lethargic and had a petechial rash. Repeat bone marrow biopsy showed dysplastic features with 5% blasts in keeping with myelodysplasia (Refractory Anaemia with Excess Blasts-1) and she was placed on close follow up. Following an episode of dental sepsis her peripheral blood film was examined and found to contain numerous myeloblast cells (Figure 1) and the presence of mitotic figures (Figure 2).

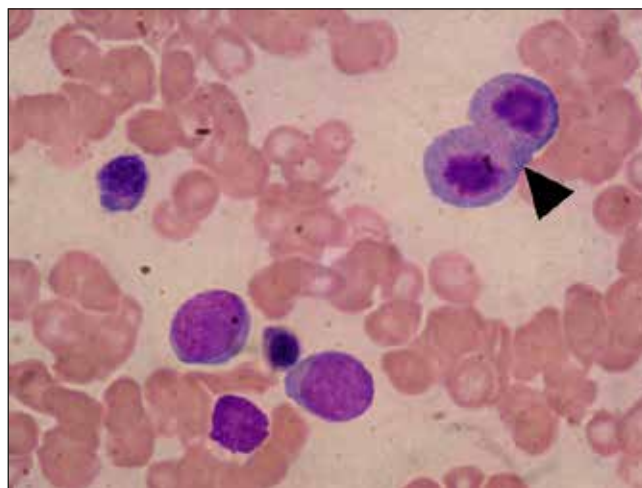


Fig 2. Mitotic figure (arrowhead) indicating high turnover rate of blast replication.

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A further bone marrow biopsy confirmed AML with a background of myelodysplasia (in keeping with therapy related AML) that was classified histologically as AML M2 (AML with maturation) in the French-American-British (FAB) classification. There were no cytogenetic abnormalities identified. Unfortunately despite chemotherapy she had unrelenting progression, became refractory to platelet transfusions and died in the hospice 9 months later, by which time her white cell count (WCC) was  $330 \times 10^9/L$ . Her death occurred 8 years after adjuvant chemotherapy for breast cancer: there was no breast cancer evident on radiological staging prior to her death.

## DISCUSSION

Breast cancer is the most common solid organ malignancy in females. Early detection with mammography screening and improvement of therapeutic options has increased survival rates. It is treated with a range of chemotherapies, radiotherapy, hormonal therapy and biological agents. Many patients receive these treatments in the adjuvant setting to decrease the risk of systemic relapse but in the context of modest survival gains from therapy. These treatments have well recognised early acute complications including neutropenic sepsis, which is occasionally fatal. However long term complications from these therapeutic modalities, especially in patients who have potentially been cured of their primary cancer, are becoming increasingly important with improved survival. Patients with breast cancer often undergo chemotherapy with repetitive bone marrow suppression which unfortunately for some can result in myelodysplastic and leukaemic syndromes. Therapy-related myeloid neoplasms (t-MN) represent a unique clinical entity in patients treated with chemotherapy or radiotherapy and unfortunately carry a poorer prognosis than *de novo* disease.<sup>1</sup>

The incidence rate of therapy-related acute leukaemia in this setting is in the order of 0.2-0.5%.<sup>1</sup> A small but real increase in AML has been reported in several larger observational studies in breast cancer follow up.<sup>2,3,4</sup> In Northern Ireland an average of 1079 cases of breast cancer are diagnosed each year. Trends confirm that the number of women diagnosed each year is increasing by an average of 23 cases per year.<sup>5</sup> At least 300 patients per year receive adjuvant chemotherapy, this could equate to one or two such cases of therapy-related AML each year, making it a potentially understated and underemphasised clinical issue.

Two main types of therapy related AML and MDS were recognised depending on the putative agent according to the 2001 WHO classification of myeloid neoplasms. These were 1) those caused by radiation or by an alkylating agent (e.g. cyclophosphamide) or 2) caused by a topoisomerase II inhibitor (e.g., doxorubicin, epirubicin). These two types have distinct phenotypes. Alkylating agent related leukaemias have a long latency (4-7 years), pre-leukaemic phase and a worse prognosis. In contrast, those induced by topoisomerase II inhibitors have a shorter latency (2-3 years median), no prodromal phase and a better prognosis<sup>6</sup> (Table

1). In this case our patient received a chemotherapy drug from both groups which is standard practice. On balance the prodromal phase and longer latency would tend to indicate that cyclophosphamide was the more significant aetiological factor.

TABLE 1.

*Key differences in therapy related AML by causative chemotherapy.*

	Alkylating Agents (eg cyclophosphamide)	Topoisomerase II inhibitors (eg doxorubicin, epirubicin)
Onset	Long latency (median time 4-7 years)	Short latency (median time 2-3years)
FAB Subtype	M1/M2	M4/M5
Preleukaemic Phase	Two thirds present with myelodysplasia, the remainder have myelodysplastic features.	No preceding myelodysplastic phase
Cytogenetic Abnormality	Chromosomal abnormalities in chromosome 5 and 7	Classically balanced translocations 11q23,21q22
Prognosis	Worse than <i>de novo</i> AML	Similar to <i>de novo</i> disease with corresponding cytogenetics

A population based study by the National Cancer Institute (NCI) analysed data for 420,000 women with breast cancer and found younger age at diagnosis and node positive breast cancer appear to confer a greater risk of AML in breast cancer survivors, potentially due to greater chemotherapy exposure or alternatively underlying genetic predisposition.<sup>7</sup> Several other factors can increase the risk of AML in this setting including: dose intensity of chemotherapy, use of adjuvant radiotherapy and the concomitant use of granulocyte colony stimulating factor (GCSF). The use of GCSF is increasing prophylactically to reduce the risk of neutropenic sepsis and includes patients receiving docetaxel chemotherapy which is a current standard of care in node-positive breast disease.<sup>8</sup>

With the increased incidence of breast cancer and the trend for more chemotherapeutic intervention in the adjuvant setting it will be of utmost importance that patients are aware of the potential risks of secondary malignancy during the consent process. This is particularly significant for younger cancer patients.<sup>9</sup> It is important to add that the therapeutic benefit from adjuvant chemotherapy in early stage breast cancer is compelling, and is of a different order of magnitude than the estimated risk of secondary leukaemia.

The authors have no conflicts of interest.

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