

## How breast cancer chemotherapy increases the risk of leukemia: Thoughts about a case of diffuse large B-cell lymphoma and leukemia after breast cancer chemotherapy

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### ABSTRACT

The latest studies suggest that prophylactic chemotherapy or adjuvant chemotherapy for early stage breast cancer may increase the leukemia risk in patients. For patients with a low risk for breast cancer recurrence, physicians who make the choice for adjuvant therapy should consider the risk of its long-term side effects. Is the occurrence of lymphatic system cancer and leukemia after breast cancer treatment associated with chemotherapy? Can these types of leukemia be classified as therapy-related leukaemias? We believe that there may be correlations between any diseases, but we cannot rush to conclusions or dismiss a correlation because we understand little about the diseases themselves. In this paper, we present a case of secondary diffuse large B-cell lymphoma and leukemia in patients after breast cancer chemotherapy, it is undeniable that this is a special event. For two distinct tumour occurrences at different times, we cannot give a clear explanation because of the changes in the genes that might link them together and we hope to attract the attention of other clinicians.

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### Introduction

With the recent progress in research and the clinical applications of endocrine therapy and molecular targeted therapy, the survival of breast cancer patients has been significantly prolonged. However, we are finding that the long-term side effects caused by chemotherapy at an early stage are also gradually becoming more prominent. The latest research by Professor Wolff Antonio has shown that prophylactic chemotherapy or adjuvant chemotherapy in patients with early stage breast cancer can increase the risk of leukemia. This study reported that the 10-year risk of lymphoid and myeloid cancer for such patients was 0.5%, approximately twice the risk observed in previous studies. However, the five-year (recurrence) risk after treatment did not decrease.<sup>1</sup> Therapy-related leukemia (TRL) has gradually become a clinical concern. However, there may be another form of leukemia on site that is due to malignant lymphoma leukemia. For such patients, if not diagnosed early, it is difficult to determine whether they have a lymphoma transformed to leukemia or leukemia invading into the lymphatic system. In this paper, a clinical case of secondary lymphoma and lymphosarcoma after breast cancer chemotherapy is reported, and its characteristics and pathogenesis are explored. We would like to draw the attention of other clinicians to these treatment-related side effects.

### Case report

A 56-year-old female patient was admitted to the first Affiliated Hospital of Dalian Medical University in September

2007 for a non-tender firm mass in the right breast. Physical examination revealed a palpable and immobile mass in the upper outer quadrant of the right breast with a diameter of approximately 3.0 cm. It was not adhered to the skin, and there was no nipple retraction, axillary lymph node enlargement, or masses in the contralateral breast. Ultrasound showed a 3.0 cm × 2.5 cm uneven hypoechoic area in the upper outer quadrant of the right breast. Therefore, we suspected that the mass was a breast tumor. The patient was eligible for surgery and had no surgical contraindications. We performed a radical mastectomy of the right breast. Pathological examination revealed a grade II-III invasive ductal carcinoma of the right breast with no lymph node metastasis and no vascular blockade by tumour cells. Immunohistochemistry revealed that the tumor was estrogen receptor (ER) 2+, progesterone receptor (PR) + and human epidermal growth factor receptor (HER) -2-. The patient was diagnosed with stage II breast cancer of the right breast. The patient received adjuvant EC (Epirubicin, EPI, Cyclophosphamide, CTX) followed by multiple rounds of T (Docetaxel, DOC), repeated for four rounds. After chemotherapy, the patient received 2.5 mg of oral letrozole daily as endocrine therapy.

In January 2011, a palpable mass was found in the left neck area. We measured the patient's carcinoembryonic antigen (CEA), cancer antigen (CA)-125, and CA-153 level, and they were all normal. Computed tomography (CT) showed no obvious abnormality in the lungs or mediastinum. There were

multiple small lymph nodes in the neck region. There was no clear sign of a breast cancer recurrence or metastasis. The patient's surgeons recommended follow-up for observation. The patient self-administered an anti-inflammatory medication, and the lymph nodes got smaller. Therefore, her symptoms were not considered serious.

Unfortunately, in May 2011, the mass in the neck mass again increased in size, along with swollen masses in the bilateral axillary and inguinal regions. CT revealed multiple swollen lymph nodes in the chest and neck. There was confluence between mediastinal lymph nodes. Follow-up testing of the breast tumour markers returned normal results. Blood routine: White blood cell  $12.73 \times 10^9/L$ , Lymphocyte  $2.69 \times 10^9/L$ , Hemoglobin  $132g/L$ , Platelet  $293 \times 10^9/L$ , Lactate dehydrogenase  $452 IU/L$ , Positron emission tomography (PET)-CT examination revealed radionuclide accumulation foci in the neck, supraclavicular, axillary, mediastinal, intra-abdominal and groin areas. The largest standardized uptake value (SUV) was 6.5. We preliminarily diagnosed the patient with a lymphoma. Pathological examination of a biopsy of a left inguinal lymph node revealed a diffuse large B-cell lymphoma. Immunohistochemistry showed CD3(-), Ki-67 > 50%, CD43(-), CyclinD1(-), CD20(+), CD5(-), CD79a(+), CD21(+), CD10(+), mum-1(-), bcl-6(+), bcl-2(+). The patient was diagnosed with a stage IIIB non-Hodgkin's lymphoma. We initially planned for R-CHOP chemotherapy, but because the patient was allergic to rituximab, two cycles of CHOP (CTX 1100 mg IV d1; EPI 120 mg IV d1; Vincristine, VCR 2 mg IV d1; Prednisone, PDN 100 mg PO Qd d1-5 q21d) chemotherapy were used, and the patient achieved partial remission (PR). The patient began to experience a fever prior to the third cycle of chemotherapy. Her body temperature fluctuated between 38 and 40°C, and blood abnormalities emerged, White blood cell  $57.12 \times 10^9/L$ , Lymphocyte  $10.54 \times 10^9/L$ , Hemoglobin  $108g/L$ , Platelet  $168 \times 10^9/L$ . We carried out a bone marrow biopsy to confirm the diagnosis. Cytological immunotyping examination of the bone marrow morphology showed bone marrow hyperplasia with abnormal lymphoid tissue accounting for 50%, uniform sizes, minimal cytoplasm, blue-coloured cytoplasm with vacuoles, visibly twisted and folded nuclei, coarse nuclear chromatin and unclear nucleoli. We considered a diagnosis of lymphoma cell leukemia. Immunotyping showed R2 accounting for 80.77% of the nucleated cells, the expression of CD10 (20.91%), CD22 (82.24%), CD20 (69.85%), CD19 (63.50%) and HLA-DR (91.39%), and the absence of CD34, CD117, CD13, CD33 and CD14 expression. Chromosomal typing showed 46,-X,-1,+7,8q+, -14,-22,+mar2,+mar3,+mar4[5]/46 and xx[5], suggesting complex chromosomal aberrations. The patient was diagnosed with a stage IIB diffuse large B-cell lymphoma and lymphoma cell leukemia.

After confirming the diagnosis, the patient received DOCP (CTX 800 mg IV d1; Pirarubicin, THP 30 mg IV d1-3; VCR 2 mg IV d1, PDN 60 mg PO Qd d1-5; Lasparaginase, LASPAR 10000 U IV Qod x 5; q21d) chemotherapy for a first cycle and with a total of two cycles planned. Due to disease progression, we replaced DOCP with CTOAP (CTX 1000 mg IV d1, THP 40 mg IV d1-3; VCR 2 mg IV d1, 8; Arabinofuranosylcytosine, Ara-C 200 mg IV d1-7; PDN 60 mg PO Qd d1-14; q21d) chemotherapy and performed intrathecal injection of methotrexate (MTX) 10 mg + 5 mg dexamethasone in 2 ml of saline to prevent central

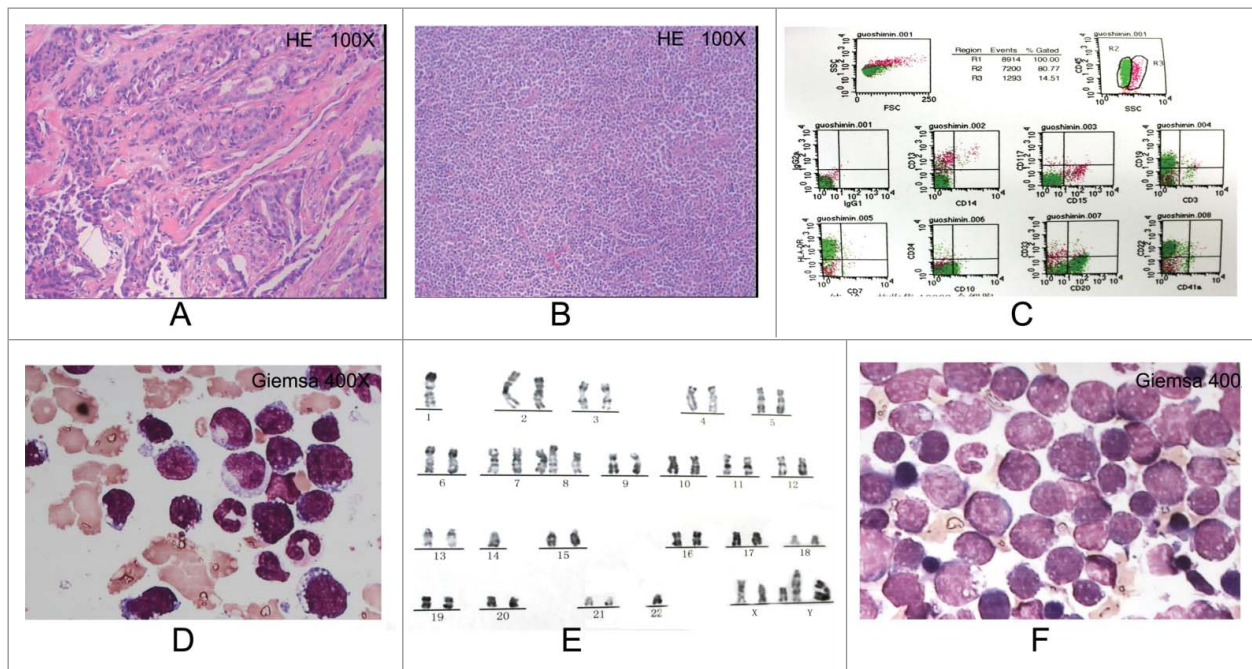
nervous system leukemia. A follow-up examination of the bone marrow cytology showed 73% lymphocytes, including 70.5% immature lymphocytes. The side effects experienced by the patient included level 4 bone marrow suppression, fatigue, weakness and anorexia. The patient refused to continue chemotherapy and received symptomatic supportive treatment before dying in the clinic in February 2012 (Fig. 1).

## Discussion

Breast cancer is one of the most common malignant tumors that have serious impacts on women's health and is often life-threatening. According to statistics published by the World Health Organization International Cancer Research Center, there were approximately 1.38 million new cases of female breast cancer worldwide in 2008, accounting for 22.9% of all female cancers. In addition, 460,000 women died of breast cancer in 2008, accounting for 13.7% of female cancer deaths.<sup>2</sup> With recent progress in neoadjuvant therapy, adjuvant therapy, endocrine therapy and targeted therapy, the survival of breast cancer patients has gradually been prolonged. However, the consequences of overtreatment have also gradually emerged. What should not be ignored are second primary cancers and TRLs. In the 1980s, TRL first gained the attention of clinicians. It is a chemotherapy-induced and/or radiation-induced leukemia due to the treatment of primary malignant or non-malignant diseases.<sup>3</sup> Professor Wolff Antonio's latest research has shown that prophylactic chemotherapy or adjuvant chemotherapy for early stage breast cancer patients can increase the risk of TRL. These findings lead us to think that the number of patients who may develop a leukemia triggered by overtreatment cannot be ignored given the large population base of breast cancer patients.

TRLs, in common clinical settings, are often in the form of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).<sup>3</sup> They are mostly direct secondary leukaemias. Diffuse large B-cell lymphomas after chemotherapy followed by transformation into lymphoma cell leukemia is rare. Should such cases be classified as TRLs? Sternberg first proposed that lymphoma cell lymphoblastic leukaemias should be classified as lymphosarcoma leukaemias. He thought that lymphoma cell leukaemias were different from leukaemias originating from general primary lymphocytes. His proposal facilitated distinguishing lymphoblastic leukaemias from other types of leukemia as a special type of leukemia that develops from a malignant lymphoma. This transition is also known as leukemic change, and this stage of lymphoma is also known as leukemic lymphoma or lymphoma cell leukemia.<sup>4</sup>

Secondary leukaemias related to breast cancer chemotherapy are commonly induced by alkylating agents or topoisomerase II inhibitors. They are generally AML and MDS and are included as an independent subtype in the standard WHO classification of haematologic malignancies.<sup>5</sup> Alkylating agents crosslink with DNA, causing gene mutations and deletions in the long arms of 5th and the 7th chromosomes. These gene mutations affect interleukin (IL)-3, IL-4 and other genes involved in cell proliferation. These deletions may activate the oncogene RAS and cause p53 tumour suppressor gene mutations, resulting in



**Figure 1.** (A) (2007-09-20) Pathological examination revealed a grade II-III invasive ductal carcinoma. (B) (2011-05-12) a left inguinal lymph node revealed a diffuse large B-cell lymphoma. (C) (2011-07-08) Immunotyping showed R2 accounting for 80.77% of the nucleated cells, the expression of CD10(20.91%),CD22(82.24%),CD20(69.85%), CD19(63.50%) and HLA-DR(91.39%). (D) (2011-07-05) Cytological immunotyping examination of the bone marrow morphology showed bone marrow hyperplasia with abnormal lymphoid tissue accounting for 50%, uniform sizes, minimal cytoplasm, blue-coloured cytoplasm with vacuoles, visibly twisted and folded nuclei, coarse nuclear chromatin and unclear nucleoli. (E) (2011-7-21) Chromosomal typing showed 46,-X,-1,+7,8q+,-14,-22,+mar2,+mar3,+mar4[5]/46 and xx[5].F:(2011-9-29) A follow-up examination of the bone marrow cytology showed 73% lymphocytes, including 70.5% immature lymphocytes.

abnormal cell proliferation and differentiation, and causing leukemia.<sup>6</sup> Topoisomerase II inhibitors form a complex with DNA and topoisomerase II, blocking the enzyme's activity and causing DNA strand breaks. These breaks occur predominantly in the acute lymphoblastic leukemia (ALL)-1 gene area, causing ALL-1 gene (MLL, Htrx 1, HRX) rearrangement and DNA damage with dehydrogenase-induced free radicals, thereby causing leukemia.<sup>7</sup> Docetaxel is a taxane anticancer drug. It binds to free tubulin and promotes tubulin assembly into stable microtubules while inhibiting their depolymerization. These effects result in the loss of normal microtubule bundle function and loss of microtubule attachment, thereby inhibiting cell mitosis. No long-term effects of docetaxel in oncogenesis and leukemia have been reported. Smith et al. analyzed 8563 clinical cases of breast cancer patients receiving CTX and anthracycline chemotherapy after surgery. They found that the occurrence rate of AML or MDS was 0.5%. The risk increased with increasing doses of CTX. The onset of AML or MDS from the time of treatment was within 1-125 months (median 38 months). Only one patient developed ALL.<sup>8</sup> Diamantidou et al. reported that, among 1107 cases of breast cancer patients who received 5-fluorouracil, doxorubicin and CTX (FAC), the incidence of AML or MDS was 1.5%, with an onset interval of 22-113 months after surgery (median 66 months). There was no incidence of ALL.<sup>9</sup> In this case, we used the EC-T program as treatment, which is a possible precursor of a diagnosis of TRL.

Unlike TRLs in the past, this case was different in that the patient had multiple swollen lymph nodes three years after chemotherapy for breast cancer. Pathological analysis of the lymph

node biopsy confirmed a diffuse large B-cell lymphoma diagnosis. However, during treatment, further changes leading to abnormal blood parameters caught our attention. Examination of the bone marrow eventually confirmed the diagnosis of lymphoma cell leukemia. Unfortunately, at the time of the initial diagnosis of lymphoma, we did not examine the bone marrow, so we are unable to report the initial bone marrow status. Because lymphoma onset may also be in the form of a leukemia and because the difference lies only in the proportion of lymphoma cells in the bone marrow, they are just different stages of one type of tumor. Of course, leukemia has a worse prognosis. Is it also possible that the chemotherapy induced a secondary TRL, which caused the leukemia and swollen lymph nodes? We did not carry out an early bone marrow examination, and we were guided by the earlier pathological diagnosis from the lymph node tissue. However, how likely is this possibility? On lymph node biopsy and subsequent pathological examination of the bone marrow, we arrived at a second diagnosis, and it remained as in the past. This result confused us, and it remains to be determined whether TRL can have an intermediate stage solid tumour status and whether lymphoma can also be caused by excessive chemotherapy and radiotherapy. Similar research reports have not offered us any hints. We only know that high-grade malignant lymphomas have a high chance of transforming into leukaemias. In particular, patients with B symptoms in the course of treatment tend to have early bone marrow involvement and extranodal involvement that is associated with the rapid development of large mediastinal masses. Treatment should be in line with the treatments for acute lymphoblastic leukemia with a poor prognosis, and the diagnosis should be distinguished from other types of leukaemia. Usually, blood

examination reveals an abnormally high number of leukocytes. Decreased red blood cell counts and hemoglobin levels are not obvious, though platelet counts are often decreased. Bone marrow cytology can reveal visible changes in the lymphatic system, mostly in the form of significant increases in the proportion of immature lymphocytes and lymphoblasts. Patients respond poorly to conventional chemotherapy due to de novo or acquired resistance. These findings are consistent with the features of this case.<sup>10</sup> However, we still cannot determine whether the lymphoma and leukemia were associated with the chemotherapy because we did not obtain conclusive evidence. However, it is undeniable that this is a special event. For two distinct tumour occurrences at different times, we cannot give a clear explanation because of the changes in the genes that might link them together.<sup>11</sup> For now, the microscopic world is still a field that we cannot fully explain.

To prevent the occurrence of TRLs, physicians should strictly control the dosing of chemotherapy drugs, particularly the dosing and administration criteria for topoisomerase II inhibitors and alkylating agents, to avoid long-term tumorigenic effects.<sup>12</sup> We believe that with increasing progress in targeted therapy and immunotherapy, more specific and non-toxic “targeted” therapies may reduce the incidence of treatment-related disease.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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