CASE REPORT

Therapy-Related Acute Myeloid Leukemia Mimicking Lymphoma: a Diagnostic Dilemma

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SUMMARY

Background: Based on the 2017 revision of the World Health Organization Classification, therapy-related myeloid neoplasms consist of therapy-related acute myeloid leukemia, therapy-related myelodysplastic syndromes, and therapy-related myelodysplastic/myeloproliferative neoplasms, which exist as a late-occurring complication of radiation and/or chemotherapy treatment due to previous application of iatrogenic mutagenic agents.

Methods: Here we present the first described case of therapy-related acute monocytic leukemia mimicking lymphoma after chemotherapy and radiotherapy for breast cancer.

Results: Based on immunophenotypic analysis and biopsy of the BM, the patient was diagnosed with acute monocytic leukemia (AML FAB M5b) according to WHO classification. Due to short interval of development, a diagnosis of therapy-related acute monocytic leukemia was made.

Conclusions: The atypical morphology of the patient, a diagnostic mistake, resulted in an initial diagnosis of secondary lymphoma. Recognizing the atypical morphology is vital in distinguishing it from lymphoma, which is closely related to the treatment and prognosis of the patient.


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KEY WORDS
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INTRODUCTION

Breast cancer is one of the most common solid organ tumors in females. Early diagnosis and improvement in treatment have increased survival rates. A range of chemotherapies, radiotherapy, biological agents, and hormonal therapy was used to treat the disease [1]. Therapy-related myeloid neoplasms (t-MNs) consist of those cases of therapy-related acute myeloid leukemia (t-AML), therapy-related myelodysplastic syndromes (t-MDS), and therapy-related myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN), which exist as a late-occurring syndrome of chemotherapy and/or radiation treatment due to previous iatrogenic application of...
mutagenic agents [2]. However, the patients of breast cancer usually undergo chemotherapy with repetitive BM suppression, which unfortunately for some patients can lead to t-MNs. T-MNs happen as a late-occurring syndrome of chemotherapy and/or radiotherapy and have a significantly poorer prognosis than de novo MNs [3]. It has been reported that breast cancer patients with younger age at diagnosis and node positive appear to have a greater risk of t-MNs in breast cancer survivors, which are mainly caused by greater mutagenic agents application or potential genetic predisposition [4]. Here, for the first time we report a case of therapy-related acute monocytic leukemia mimicking lymphoma after chemotherapy and radiotherapy for breast cancer, which may lead to the morphological variation of acute monocytic leukemia compared with de novo AML (M5b).

CASES PRESENTATION

A 41-year-old female was initially diagnosed with infiltrating ductal carcinoma of the right breast. Induction chemotherapy was performed using doxorubicin, cyclophosphamide for eight cycles after modified radical operation and intermittent radiotherapy during this period. Twenty-six months after the initial diagnosis, the patient presented with recurrent fever for 10 days and reddish nodules on the left shoulder and back. Blood work showed leukopenia and anemia (hemoglobin, 74 g/L; white blood cells, 1.1 x 10⁹/L; platelets, 138 x 10⁹/L). Peripheral smears stained by Wright-Giemsa showed lymphoma-like blasts occasionally. Bone marrow smears revealed diffuse invasion by sheets of lymphoma-like blasts, which displayed fine chromatin, rich basophilic cytoplasm and distinct cytoplasmic pseudopodia (Figure 1a - d). The blasts were negative for myeloperoxidase (MPO). Flow cytometry revealed an abnormal myeloid population. The cell population was positive for CD13, CD38, CD33, CD117, CD123, HLA-DR, a few cells expressed CD34, CD7, CD36, and the blasts were weakly positive for MPO (Figure 2). BM biopsy indicated diffuse proliferation of big-sized blasts with round or irregular nucleus, abundant cytoplasm, and clear nucleoli. Immunohistochemical stain indicated that the blasts were positive for lysozyme, a few blasts were positive for CD117 and CD163, and the blasts were positive for MPO, CD3, CD19, and CD34. Cytogenetic analysis indicated a 46,XX [6] karyotype. A mutation of the TP53 gene was detected, and no mutations were detected in genes including ASXL1, CEBPA, FLT3-ITD, FLT3-TKD, IDH1, IDH2, KIT, KRAS, NPM1, NRAS, PTPN11, RUNX1, and WT1. Based on immunophenotypic analysis and biopsy of the BM, the patient was diagnosed with acute monocytic leukemia (AML FAB M5b) according to WHO classification [5]. However, the morphological and MPO staining features led to an initial diagnosis of lymphoma. Thus, we called the condition t-AML mimicking lymphoma. Subsequently, non-specific esterase staining of bone marrow smears was performed, and the blasts were positive for non-specific esterase, which were obviously inhibited by sodium fluoride. The result confirmed the diagnosis of acute monocytic leukemia. Due to the short interval of development, a diagnosis of therapy-related acute monocytic leukemia was made. Unfortunately, despite chemotherapy the patient died one year after t-AML was established as a result of further disease progression and no evident breast cancer on radiological staging prior to her death.

DISCUSSION

Two subsets of t-MNs are extensively recognized clinically. The more frequent form happens 5 - 10 years after application of ionizing radiation and/or alkylating agents, which are usually characterized by bone marrow failure and MDS. Another happens within 1 - 5 years after therapy with agents that are associated with DNA topoisomerase II, which manifests as t-AML or t-MDS/MPN. The diagnosis of t-MNs is usually poor, especially for cases presenting with TP53 mutations, abnormalities of chromosomes 7 and/or 5, and a more complex karyotype. They commonly have a median survival less than one year, regardless of manifestation as a t-MDS or t-AML [6-7]. Linassier et al. [8] reported ten t-AML patients after being treated with anthracyclines, cyclophosphamide, fluorouracil, and radiation therapy for breast cancer. They concluded that anthracyclines were the responsible agent for therapy related acute leukemia because the AML type of the cases was different from that described with alkylating agents. Most of their cases had a poor prognosis due to recurrence or complications. However, Quesenel B et al. [9] reported inversion of chromosome 16 was related with a better prognosis. Due to short interval of development and no preceding myelodysplastic period, t-AML of the patient was likely induced by a topoisomerase II inhibitor (anthracyclines), which may lead to the morphological variation of acute monocytic leukemia compared with de novo AML (M5b). We speculated that the poor prognosis of the patient was closely related to the atypical morphological features and TP53 gene mutation.

The atypical morphology and confused cytochemical staining of the patient as a diagnostic pitfall resulted in initial diagnosis of secondary lymphoma, and recognizing the atypical morphology is significant in distinguishing it from lymphoma, which is closely related to the treatment and prognosis of the patients. Flow cytometry and BM biopsy play an important role in myeloid blast establishment of the patients with misleading morphology.
Figure 1. Bone marrow smears revealed diffuse invasion by sheets of lymphoma-like blasts, which displayed fine chromatin, rich basophilic cytoplasm, and distinct cytoplasmic pseudopodia (a-d, Wright-Giemsa, x 1,000).

Figure 2. The cell population was positive for CD13, CD38, CD33, CD117, CD123, HLA-DR, a few cells expressed CD34, CD7, CD36, and the blasts were weakly positive for MPO.
CONCLUSION

Morphology of the cells is an important, but increasingly less significant tool. It is only one column in the whole diagnostic process. The combination of clinical, morphological, immunophenotypic, and genetic features ensures a correct diagnosis. In addition, we emphasize that optimization and improvement of therapy protocol and intensity can reduce the risk of a t-MN. It is vital for doctors and the lab staff to differentiate it from de novo AML and secondary lymphoma, which is related with therapy protocol and prognosis of the patients.

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This article does not contain any studies with human participants performed by any of the authors.

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All authors declare that they have no conflict of interest.

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