Case Report

Drug-Induced Interstitial Lung Disease after Anthracycline-Combined Chemotherapy for Breast Cancer: A Case Report and Literature Review

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Keywords

Drug-induced interstitial lung disease · Interstitial pneumonia · Breast cancer · Anthracycline · Prednisolone

Abstract

Drug-induced interstitial lung disease (DILD) has been occasionally reported with various causative drugs. In the context of breast cancer, anthracycline infrequently causes pulmonary adverse events. We report a 67-year-old woman with cT2N0M0 triple-negative breast cancer who received neoadjuvant chemotherapy with anthracycline-combined chemotherapy with pegfilgrastim. She developed fever, cough, and shortness of breath after 21 days of the scheduled fourth cycle of anthracycline. Computed tomography revealed drug-induced interstitial pneumonia. Prednisolone (1 mg/kg) was administered and gradually decreased. Thereby, interstitial pneumonia quickly improved. Partial resection of the left breast and sentinel lymph node biopsy were performed, and we diagnosed ypT1bN0. The patient received 4 cycles of taxane and hypofractional radiotherapy and survived without any recurrences over the following 37 months. We report a rare case of DILD due to anthracycline-combined chemotherapy. Twenty-five cases of DILD with breast cancer after administration of anthracycline have been reported so far. However, 14 cases occurred during taxane. Most of the cases had remission by steroid treatment. The patients with respiratory symptoms during chemotherapy should be suspicious of not only infection but also DILD.

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Introduction

The occurrence of drug-induced interstitial lung disease (DILD) is associated with the use of several classes of drugs. For patients with cancer who undergo chemotherapy, temporary amelioration of DILD is important so that the treatment for cancer can be continued.

In the field of breast cancer, some new causative drugs such as antibody-drug conjugates, molecular targeted drugs, and immune checkpoint inhibitors have been reported. The trastuzumab-conjugated deruxtecan was reported to cause DILD in 13.6% of patients [1], whereas everolimus was reported to cause DILD in 22% of patients [2]; furthermore, atezolizumab, an anti-programmed death-ligand 1 antibody, was reported to cause DILD in 3.5% of cases [3]. On the contrary, several chemotherapy drugs have also been reported to induce DILD. The key drug for breast cancer belongs to the anthracycline class, such as epirubicin and doxorubicin, which is used in combination with cyclophosphamide or 5-FU. This anthracycline-combined chemotherapy is reported to have rarely induced DILD (<1% of cases) [4].

Herein, we report a rare case of DILD after anthracycline-combined chemotherapy. The patient was quickly relieved from DILD with prednisolone (PSL) treatment and underwent breast-conserving surgery, followed by adjuvant taxane and radiotherapy.

Case Report/Case Presentation

A 67-year-old Japanese woman visited the outpatient clinic with complaints of a palpable mass and pain in her left breast. She had a medical history of surgeries for appendicitis and ovarian cyst and no family history. Upon clinical examination, the hard mass was palpable in the left breast, and no other abnormal findings were identified in either breast. Mammography and ultrasonography scans revealed a spiculated mass with polymorphic calcifications, which were indicative of breast cancer, and no enlarged lymph nodes in the axilla. Radiographic test results were negative for distant metastases. The clinical stage was stage IIA (T2 N0 M0). A core needle biopsy revealed an invasive lobular carcinoma of 30 mm in maximal diameter with nuclear grade 3. The tumor cells were negative for the estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and E-cadherin. The Ki67 labeling index was high at 50%. Combined chemotherapy with 500 mg/m² fluorouracil, 100 mg/m² epirubicin, and 500 mg/m² cyclophosphamide (FEC) every 3 weeks followed by 75 mg/m² docetaxel every 3 weeks was planned to be administered in the neoadjuvant setting to perform breast-conserving surgery and to achieve the necessity of adjuvant chemotherapy.

Four cycles of FEC using pegfilgrastim were performed without disruption. Febrile neutropenia had not occurred. At 21 days after the administration of the fourth cycle of FEC when docetaxel was intended to be administered, she complained of fever (body temperature of 37.3°C), dry cough, and shortness of breath. She had a performance status score of 1 and a blood oxygen saturation rate of 98%. CT findings revealed nonregional interstitial pneumonia with a diffuse crazy-paving appearance suggestive of DILD (shown in Fig. 1a). Infectious pneumonitis and DILD due to anthracycline or other drugs should be differentiated. Laboratory tests revealed a neutrophil count of 4,004/μL, C-reactive protein level of 6.46 mg/dL (normal range, <0.3), and lactate dehydrogenase level of 321 IU/L (normal range, 115–245), which were consistent with DILD. The administration of a scheduled docetaxel to the patient was temporarily terminated, and the patient was treated with a corticosteroid, oral PSL (1 mg/kg). Abnormal radiologic findings of the lung and the symptoms quickly improved and did not recur with decreasing doses of PSL. The abnormal CT findings disappeared on day 14 since PSL administration (shown in Fig. 1b). The patient underwent partial mastectomy of the left breast and sentinel lymph node biopsy. She was diagnosed with pathological-stage IA (ypT1b N0 M0)

Fig. 1. Chest computed tomography image showing nonregional interstitial lung disease (**a**). After prednisolone administration for 14 days, these radiographical signs almost disappeared (**b**).

breast carcinoma. The histological response of chemotherapy was grade 2a, and the Ki67 labeling index decreased by <5%. The patient was additionally treated with 4 cycles of docetaxel with pegfilgrastim and hypofractionated radiotherapy targeted to the left breast. The patient survived without any recurrence for 37 months after DILD.

Discussion/Conclusion

Various types of drugs are reported to cause DILD. In the present case, anthracycline, cyclophosphamide, 5-FU, or pegfilgrastim was a candidate causative drug of DILD. Although a rare case of DILD due to cyclophosphamide or oral 5-FU called S-1 also was reported [5, 6], the chemotherapy for breast cancer is usually combined with anthracycline and cyclophosphamide or 5-FU [4]. It was finally confirmed that DILD in the present case was due to anthracycline-combined chemotherapy because after surgery, the patient underwent 4 cycles of docetaxel with pegfilgrastim and did not experience DILD.

The diagnosis of DILD requires typical findings of radiographic tests such as high-resolution CT [7]. To support the diagnosis, investigations on serum markers such as Krebs von den Lungen-6 are useful. The mechanisms of DILD differ between cytotoxic and immune-mediated pulmonary injuries [8]. Cytochrome P450, an oxidative metabolizing enzyme, plays a significant role in cytotoxic pulmonary injury because it is related to drug metabolism and drug concentration in individuals. In immune-mediated pulmonary injury, drug allergy plays a significant role, and a drug-induced lymphocyte stimulation test conducted *in vivo* can sensitively detect DILD. In oncological phase I trials, Yonemori et al. [9] reported that the overall incidence rate of DILD was 0.77% (grade 3 or 4, 0.31%), the median time to occurrence was 1.4 months, and the odds ratio for radiation therapy in combination with molecular targeted agents or cytotoxic agents was 11.39 (95% confidence interval: 3.408–38.076).

We conducted a literature search in PubMed using the keywords “breast cancer and interstitial lung disease” and “breast cancer and interstitial pneumonia” on September 30, 2021. We also checked the references cited in the original articles and excluded some articles in which the authors confirmed that other drugs were more likely to be causative agents than anthracycline. Twenty-six cases of DILD after anthracycline administration for breast cancer were finally identified, including our case [10–15] (Table 1). Abnormal CT findings were detected

Table 1. Cases of drug-induced interstitial lung disease after anthracycline administration

References	Huober et al. [10]	Mark and Thürlimann [11]	Kawajiri et al. [12]	Omoto et al. [13]	Meng et al. [14]	Tezuka et al. [15]	Present case
Year	2010	2012	2013	2019	2020	2021	2021
Age, yr	53	70	45	60	63	65	67
Sex	Female	Female	Female	Female	Female	Female	Female
Stage of breast cancer	IV	IV	IIIA	IIA	IIIA	IIB IIA 2 IIB 2 IIIA 1	Stage IIA
Subtype of breast cancer	NR	NR	Luminal	Luminal	NR	Luminal 4 TNBC 1	TNBC
Type of anthracycline	PLD	PLD	FEC	EC	PLD	Dose-dense EC	FEC
Combination drugs	BEV	None	Followed by wPTX 4	None	Without DCT 4 With DCT 8	Followed by wPTX 2	None
Treatment	PSL	Steroid and antibiotic	MPSL	MPSL	Steroid	PSL TMP/SMX	PSL TMP/SMX
Diagnosis modality	CT	CT	NR	CT		CT	CT
Weeks to incidence	6	16	11	9	3	4	12
Prognosis	Remission	Death	Remission	Remission	Remission	Remission	Remission

NR, not reported; TNBC, triple-negative breast cancer; PLD, pegylated liposomal doxorubicin; FEC, fluorouracil, epirubicin, and cyclophosphamide; BEV, bevacizumab; wPTX, weekly paclitaxel; DCT, docetaxel; PSL, prednisolone; MPSL, methylprednisolone; TMP/SMX, trimethoprim-sulfamethoxazole.

in all cases, and anthracycline was administered until the confirmed diagnosis of DILD. However, 14 patients (53.8%) experienced DILD several times after the administration of paclitaxel or docetaxel following anthracycline. In these cases, taxanes were the possible cause for DILD development. Most patients were treated with steroids, which resulted in remission. Only 1 patient died due to DILD, and 2 patients simultaneously experienced pneumonia due to *Pneumocystis jirovecii*.

DILD occurrence due to anthracycline use is rare. However, patients with respiratory symptoms after anthracycline-combined chemotherapy should be considered for a suspected diagnosis of DILD.

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Statement of Ethics

This study is exempt from ethics committee approval because the case report is granted an exemption from requiring ethical approval at our hospital. We have written it according to the CARE checklist 2013. Written informed consent was obtained from the patient prior submitting. Written informed consent was obtained from the patient for publication of this case report and any accompanying images by H.H.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.H. designed the study in accordance with the CARE checklist 2013. H.T. edited the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in PubMed, Reference No. [10–15].

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