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CASE REPORT

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# Case report of radiation-induced lung injury with trastuzumab emtansine: the lung also matters

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## ABSTRACT

With an increase in the number of agents used concurrently with radiotherapy (RT), a new research area has emerged regarding toxicity. Here, we present a case of a 47-year-old woman presenting with radiation-induced lung injury (RILI) that occurred six months after the end of RT with concomitant and sequential use of trastuzumab-emtansine (T-DM1) with RT. The patient's T-DM1 treatment was discontinued because of RILI. Antibiotic and methylprednisolone treatments were started. The steroid dose was gradually tapered and completely discontinued after full recovery. If new agents are used concurrently with RT, the toxicity profile of new agents should be kept in mind.

**Key words**: breast cancer, trastuzumab emtansine, pneumonitis, radiotherapy

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## Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for approximately 20% of all breast cancers and is associated with aggressive clinical behavior and poor prognosis [1]. The use of anti-HER2 therapies including trastuzumab, pertuzumab, lapatinib, neratinib, and trastuzumab-emtansine (T-DM1) has resulted in extended survival in patients with HER2-positive breast cancer [2] In a systematic review by the European Organization for Research and Treatment of Cancer Quality of Life Group, it was shown that side effects were more common for patients treated with anti-HER2-targeted therapies other than trastuzumab or with dual-HER2 regimens and for patients with metastatic disease. Diarrhea and skin rash were the most prevalent symptoms, experienced by 29% and 22% of patients, respectively. On the other hand, the risk of cardiac events was reported to be 2% [3]. Lung toxicity in these patients has been little mentioned in the literature, however, drug-induced lung disease encompasses a group of serious, and sometimes life-threatening pulmonary conditions characterized by fibrosis and inflammation of the lung interstitium [4].

Radiation-induced lung injury (RILI) was first described at the end of the 19$^{th}$ century and is usually defined as the dose-limiting factor for thoracic and breast radiotherapy (RT) [5]. It is defined radiologically by sharply demarcated parenchymal opacity and traction bronchiectasis that is located in the RT fields. Most patients with RILI have asymptomatic radiological findings of pneumonitis, and symptomatic cases have dyspnea, nonproductive cough, or a low-grade fever [6]. The risk of grade 2 or higher radiation pneumonitis due to RT for breast cancer has been shown to be in the range of 1–9% depending on the RT dose and fractionation,

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amount of lung tissue in the treatment field, use of predisposing chemotherapy, concomitant use of selective estrogen receptor modulators (SERMs), and the extent of regional nodal irradiation (RNI) [7].

In recent years, the number of agents used concurrently with RT in breast cancer has increased, and the toxicity that may occur with these agents has become a new research area. T-DM1 used either concurrently or sequentially with RT, promptly entered oncology daily practice with a proven 50% risk reduction in recurrence and death in the landmark KATHERINE trial [8]. The risk of developing pneumonitis with T-DM1 has been reported to be in the range of 0.1–1.1% in the literature [9]. However, there is no clear data in the literature regarding the risk of developing pneumonitis when RT is combined with T-DM1. In this report, we will present an uncommon case of RILI precipitated by using T-DM1 with RT concurrently and sequentially.

## Case report

In January 2021, a 47-year-old previously healthy Caucasian female patient was diagnosed with a cT-2N3bM0, estrogen, and progesterone receptor negative, HER2 positive, grade 3 invasive ductal carcinoma of the right breast. A course of neoadjuvant chemotherapy with 4 cycles of dose-dense doxorubicin-cyclophosphamide and 4 cycles of docetaxel-pertuzumab-trastuzumab was administered, which was followed by breast-conserving surgery and axillary lymph node dissection. The pathological evaluation revealed 1.5 cm residual invasive ductal carcinoma with grade 3 histology. All the surgical margins were free of the tumor. One lymph node was with macro-metastasis but without extracapsular extension. The remaining 13 lymph nodes were tumor free. Between 21.01.2021 and 09.03.2021, we applied a course of external beam RT with conventional daily fractionation to a total dose of 50 Gy to the whole right breast, supraclavicular (SC) fossa, level 3 axilla, and internal mammary lymphatics followed by a boost dose of 16 Gy to the primary tumor site. RT was in the form of volumetric modulated arc therapy (VMAT) technique (Fig. 1), and total lung doses were 52%, 31%, and 20% for the volume of the lungs that received 5 Gy (V5), 10 Gy (V10), and 20 Gy (V20), respectively. RT was well tolerated with only grade 1 dermatitis. During RT, she was prescribed T-DM1 with 3.6 kg/mg every three weeks and was put on the continuation of T-DM1 treatment after RT.

Six months later, she was admitted to our clinic with complaints of dyspnea and non-productive cough. The physical examination revealed coarse respira-

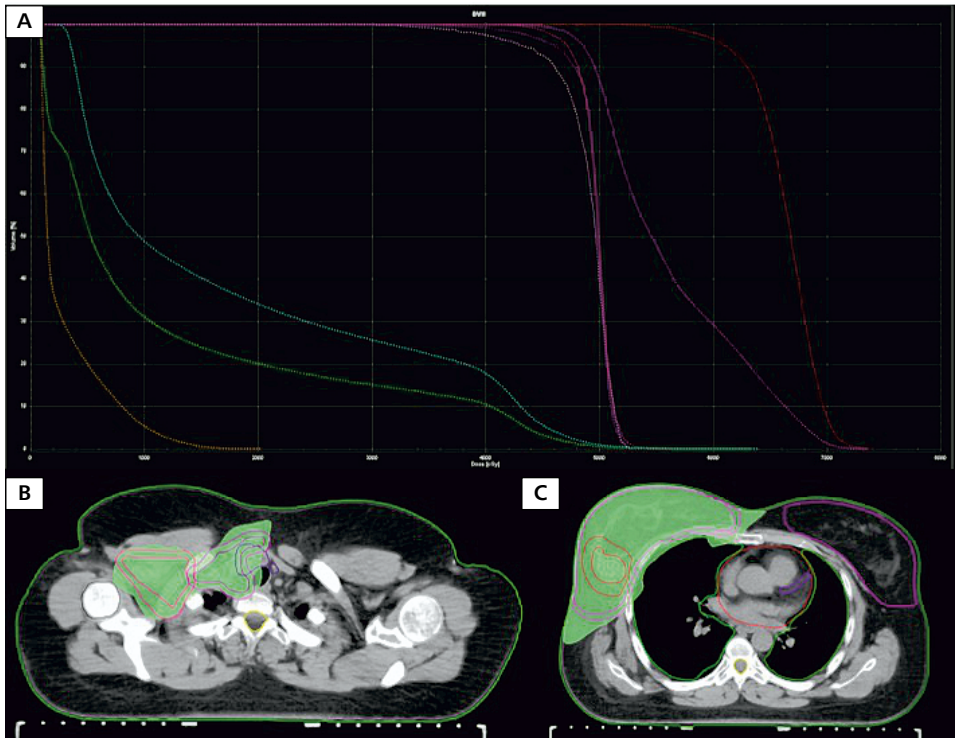


**Figure 1A.** Cumulative dose-volume histogram (red and pink lines: PTV right breast, MI, Level 1–2–3 axilla and supraclavicular fossa), blue line: right lung, orange line: left lung, green line: bilateral lung; **B, C.** Axial view of treatment plan (Green isodose volume: 45 Gy)

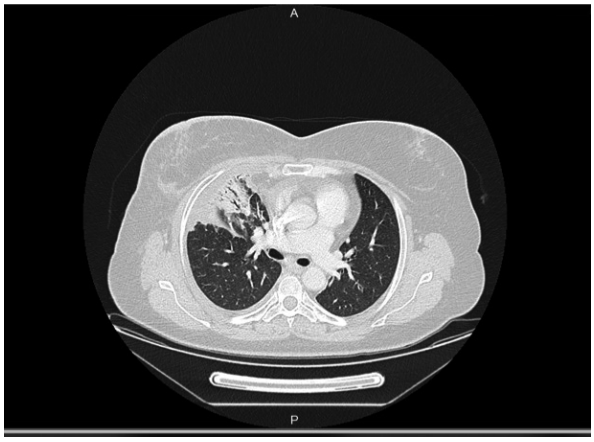


**Figure 2.** Computed tomography scan of the chest showing radiation-induced lung injury.

tory sounds and tachypnea. Three consecutive blood, throat, sputum, and bronchoalveolar lavage cultures, and acid-fast bacillus staining were all negative. The COVID-19 test result was negative. Computed tomography (CT) scan of the thorax demonstrated infiltrates with enlarged air bronchograms in the right lung middle lobe and upper lobe anterior segment, which was compatible with radiation pneumonitis (Fig 2). The patient's T-DM1 treatment was discontinued, and 1 mg/kg of methylprednisolone and antibiotic treatment was started. Symptoms regressed within seven days. Steroid treatment was tapered slowly over 2 months and consequently stopped following complete recovery. After recovery, T-DM1 treatment was not restarted, and the patient received a total of ten cycles of adjuvant T-DM1.

Written informed consent was obtained from the patient for publication of this case report.

## Discussion

In this particular report, we present a case of a patient who developed pneumonitis mainly located in the radiation fields 6 months after RT. She was being treated with T-DMI concurrently and sequentially with RT. There were no predisposing conditions that might have precipitated the RILI, such as smoking history or interstitial lung disease, and the dose-volume parameters of the lungs were below the limits according to the generally accepted recommendations [10]. Our patient had both clinical symptoms and typical radiological findings of RILI. While ground-glass opacities or consolidation are seen in the acute phase of RILI, consolidation, traction bronchiectasis, and volume loss develops in the later phase of RILI, similar to our patient's presentation [6].

Ado-trastuzumab, also called T-DM1, was initially approved by the Food and Drug Administration (FDA) to treat women with metastatic HER2-positive breast cancer [11]. The FDA expanded the approved use of the drug to treat women with HER2-positive breast cancer on the adjuvant basis in 2019 based on the positive results of the KATHERINE trial [12]. The risk of recurrence and death is reduced by using adjuvant T-DM1, instead of adjuvant trastuzumab, in patients with residual disease after completion of neoadjuvant chemotherapy combined with anti-HER2 therapy (I, A; ESMO-MCBS v1.1 score: A) [13].

In the KATHERINE trial [8] including women with residual cancer after neoadjuvant therapy, T-DM1 on the adjuvant basis brought a 50% reduced risk of recurrence or death compared to women treated with trastuzumab. Adverse events of any grade were more common in the T-DM1 group than in the trastuzumab group: 25.7% of the patients had adverse events of grade 3 or higher in the T-DM1 group, and 15.4% in the trastuzumab group. Pneumonitis (of any grade) was reported in 19 patients in the T-DM1 group (2.6%) and 6 patients in the trastuzumab group (0.8%).

Though there are very limited data regarding the unexpected frequency and magnitude of toxicity of this drug when used with RT, an increased rate of radiation dermatitis and radiation pneumonitis with TDM-1 has been reported before [8, 14]. Of the adverse events of any grade in the KATHERINE trial, 1.5% in the T-DM1 and 0.7% in trastuzumab groups were radiation pneumonitis (8). Microtubule inhibitors, such as taxanes and vinca alkaloids, have very-well known radiosensitizing efficacy when used concomitantly with RT [15]. T-DM1 is a therapeutic agent that combines the monoclonal antibody trastuzumab with the cytotoxic mertansine (DM1), a maytansinoid class anti-microtubule agent, linked by a stable thioether [16]. The increase in radiation pneumonitis when used concomitantly with TDM-1 may be due to the anti-microtubule agent DM1.

Radiation pneumonitis after RT for breast cancer has been reported to be related to the following factors: the amount of lung irradiated within the tangential fields, the use of an additional SC field, prior exposure to chemotherapy as anthracyclines and taxanes, and concurrent SERMs and smoking habits. RT to the chest wall results in < 1% incidence of radiation pneumonitis, and with RNI it increases up to 11% [17]. However, with the advent of new techniques, such as intensity-modulated RT (IMRT), the risk of radiation pneumonitis decreased significantly in recent years. In a study by Ho et al. [18], the overall rate of respiratory toxicities was 10.6%, with only a 0.96% risk of symptomatic radiation pneumonitis with the inverse planning IMRT technique in patients receiving RNI. As far as we know, there are no prospective data regarding the risk of developing symptomatic radiation pneumonitis in patients treated with T-DM1 concurrently with IMRT to the chest wall/breast with or without RNI. Recently, local treat-

ment and toxicity results of the phase II ATEMPT study, comparing adjuvant T-DM1 (n = 383) and paclitaxel and trastuzumab (n = 114) in 497 patients with stage I HER2 positive breast cancer, were published [19]. Pneumonitis after RT was observed in 1% of patients in the T-DM1 arm: 0.8% had grade 2 and 0.3% had grade 3. In that study, only 1.3% of cases in the T-DM1 arm were treated with a separate nodal field. While whole breast irradiation and tumor bed boost were applied in the case of a patient who developed grade 3 pneumonia, conventional RT was applied in the other three cases of patients with grade 2 pneumonia, in whom two had a separate nodal field. In our case, the use of T-DM1 after extended field RT (including mammaria interna) might have predisposed the patient to RILI. Therefore, in patients with an indication for T-DM1 and RT, caution should be taken in terms of RILI, and the patient's lung doses should be kept as low as possible, especially in patients requiring RNI.

With the introduction of new systemic agents into the oncology landscape, patients indisputably live longer. It is important to evaluate the side effects of these new agents on normal tissues as they will affect the long-term quality of life of patients. The interaction of RT, which is an indispensable part of multimodal therapy, with new agents and the toxicity profile should be kept in mind, and these patients should be followed closely. Therefore, radiation oncologists should play a role in the design and evaluation of the results of landmark studies that introduce new agents to our oncology practice (14). Success in oncological treatments can only be achieved with a decrease in the side effects. Clinicians should be on alert for rare side effects such as pulmonary toxicity and early diagnosis, and treatment should be tailored based on an individual basis.

Under these circumstances, it would be right to hypothesize that usage of T-DM1 may increase the susceptibility to radiation pneumonia. In fact, this situation can also be called radiation recall pneumonitis [20]. Adjuvant T-DM1 usage might trigger the development of inflammatory reactions throughout previously irradiated lung tissue. Although dermatitis is the most common clinical manifestation of the radiation recall phenomenon, patients may present with visceral reactions including pneumonitis. However, it is very difficult to distinguish whether this is RILI or T-DM1-induced radiation recall pneumonitis.

## Conclusions

In this article, we emphasized the importance of considering increased side effects that may occur in the concurrent/sequential use of new systemic agents and RT. Involving radiation oncologists in the process of introducing new agents into oncology practice can prevent side effects that may be precipitated by concurrent regimens.

## Conflict of interest

Authors declare no conflict of interest.

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## Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

## Ethical approval

Hacettepe University does not require ethical approval for reporting individual cases or case series.

## Guarantor

MG.

## Contributorship

EG and MTY wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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