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Recurrent Secondary Organizing Pneumonia During Adjuvant Letrozole Therapy Following Breast Cancer Radiotherapy: A Case Report

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Abstract

Aromatase inhibitors are a cornerstone of adjuvant endocrine therapy for hormone receptor-positive breast cancer and are generally associated with a favorable safety profile. However, rare pulmonary toxicities, including organizing pneumonia, have been sporadically reported.

Secondary organizing pneumonia (SOP) is an uncommon inflammatory pulmonary disorder that may occur in association with infections, autoimmune diseases, radiation exposure, or drug-induced toxicity. We report the case of a 69-year-old woman who developed recurrent SOP during adjuvant letrozole therapy following surgery, chemotherapy, and locoregional radiotherapy for hormone receptor-positive early-stage breast cancer. The patient presented with bilateral pulmonary infiltrates characterized by ground-glass opacities and consolidative changes, predominantly involving previously irradiated lung regions. Extensive diagnostic evaluation excluded infectious, malignant, and other potential etiologies.

Initial treatment with systemic corticosteroids resulted in rapid clinical and radiological improvement. However, multiple relapses occurred during corticosteroid tapering while letrozole therapy was continued. Following multidisciplinary evaluation and discontinuation of letrozole, complete radiological resolution was achieved, and no further recurrences were observed during follow-up.

The temporal relationship between letrozole exposure, recurrent inflammatory pulmonary manifestations, repeated corticosteroid responsiveness, and sustained recovery after drug withdrawal suggests a possible association between letrozole therapy and SOP. Prior thoracic irradiation may have contributed to increased susceptibility to pulmonary injury. Although the underlying mechanisms remain poorly understood, immune-mediated pathways and persistent inflammatory activation within previously irradiated lung tissue may play a role.

This case highlights the importance of considering aromatase inhibitor-associated organizing pneumonia in breast cancer survivors presenting with recurrent pulmonary infiltrates, particularly when symptoms recur despite corticosteroid therapy and alternative causes have been excluded.

Categories: Radiation Oncology, Oncology, Pulmonology
Keywords: breast cancer, ground-glass opacities, letrozole, secondary organizing pneumonia, thoracic irradiation

Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide [1], and hormone receptor-positive/HER2-negative invasive ductal carcinoma represents the predominant molecular subtype [2]. Adjuvant endocrine therapy with aromatase inhibitors significantly reduces recurrence risk and improves survival outcomes in postmenopausal patients with hormone receptor-positive disease [3].

Although aromatase inhibitors are generally well tolerated, rare pulmonary toxicities, including interstitial lung disease and organizing pneumonia, have been reported [4]. Letrozole-associated organizing pneumonia appears to be exceptionally uncommon, with only a limited number of published cases currently available in the literature [5]. Because the clinical and radiological manifestations are often nonspecific, diagnosis may be challenging and requires careful exclusion of infectious, malignant, and other inflammatory etiologies.

The diagnostic evaluation may be particularly complex in patients previously treated with thoracic radiotherapy. Radiation-induced organizing pneumonia (RIOP) is a recognized, although uncommon, complication of breast irradiation and may present with clinical and radiological features that overlap substantially with drug-induced organizing pneumonia [6]. Distinguishing between these entities is often difficult, particularly when endocrine therapy and radiotherapy have been administered within the same treatment course.

We report the case of a 69-year-old woman with stage II hormone receptor-positive breast cancer who developed recurrent secondary organizing pneumonia during adjuvant letrozole therapy following surgery, chemotherapy, and locoregional radiotherapy. The clinical course was characterized by repeated relapses during corticosteroid tapering while letrozole therapy was continued and sustained resolution following drug discontinuation. This case highlights the importance of recognizing rare endocrine therapy-associated pulmonary toxicities and raises the possibility that prior thoracic irradiation may increase susceptibility to inflammatory lung injury in selected patients.

Case Presentation

A 69-year-old woman was diagnosed with right-sided breast cancer in May 2023. Histopathological examination demonstrated invasive ductal carcinoma, grade 2 (G2). Immunohistochemical analysis revealed estrogen receptor (ER) expression of 100%, progesterone receptor (PR) expression of 100%, HER2 1+, and a Ki-67 proliferation index of 15%.

The patient underwent right breast-conserving surgery with axillary lymph node dissection. Final pathology demonstrated a 21-mm invasive ductal carcinoma with negative surgical margins (1 cm). Metastatic involvement was identified in 2 of 15 axillary lymph nodes, corresponding to pT2N1a, L1/Pn1, R0, stage II disease according to the AJCC TNM 8th edition.

The patient subsequently received four cycles of adjuvant chemotherapy with docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2) administered every three weeks, followed by locoregional radiotherapy. Endocrine therapy with letrozole was initiated concurrently with radiotherapy. From November 2023 to December 2023, adjuvant radiotherapy was delivered to the right breast and regional lymph nodes at a dose of 2.66 Gy per fraction for 16 fractions (total dose 42.56 Gy), followed by a tumor-bed boost of 2.5 Gy per fraction for 4 fractions (total dose 10 Gy).

In January 2025, approximately 14 months after initiation of letrozole therapy and after completion of adjuvant RT, the patient presented with dry cough, low-grade fever, dyspnea on exertion, and generalized weakness. Vital signs revealed a respiratory rate of 22 breaths/min, a heart rate of 90 beats/min, and an oxygen saturation (SpO_2) of 92% on room air, which further decreased to 89% following ambulation.

Chest computed tomography (CT) demonstrated bilateral ground-glass opacities and consolidative infiltrates, predominantly involving the right lung and previously irradiated regions (Figure *1A*). The radiological findings were considered suggestive of organizing pneumonia. The differential diagnosis included infectious pneumonia, radiation-induced organizing pneumonia, and drug-induced pulmonary toxicity [7].

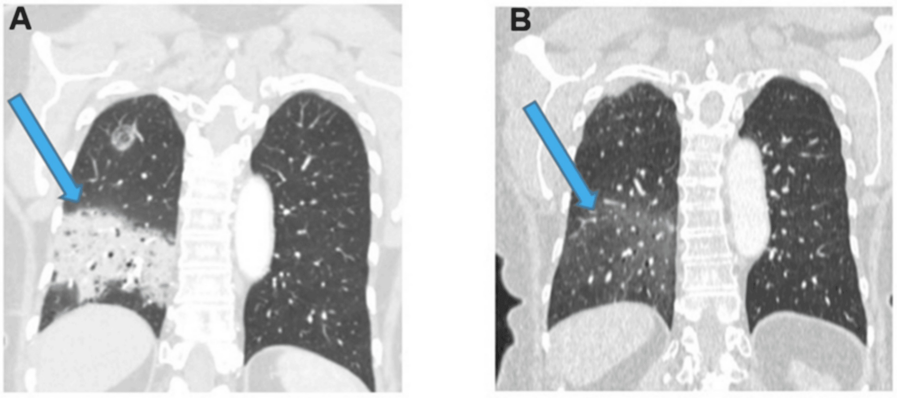


FIGURE 1: Chest computed tomography (CT) findings before and after corticosteroid treatment.

(A) Coronal CT image at presentation demonstrating bilateral pulmonary infiltrates characterized by consolidative and ground-glass opacities, predominantly involving the right lung and corresponding to previously irradiated regions. (B) Coronal CT image obtained four weeks after initiation of methylprednisolone therapy demonstrating marked radiological improvement, with near-complete resolution of the previously observed infiltrates and only minimal residual ground-glass changes.

Laboratory investigations revealed a normal white blood cell (WBC) count of 7.1 × 10^3/μL (reference range: 1.0-10.0 × 10^3/μL) and an absolute neutrophil count of 2.3 × 10^3/μL (reference range: 1.5-7.7 × 10^3/μL). Despite these normal findings, C-reactive protein (CRP) was markedly elevated at 243 mg/L (reference range: 0-5 mg/L), while procalcitonin remained within the normal range at 0.13 ng/mL (reference range:

0.00-0.15 ng/mL).

In January 2025, serum *Aspergillus* antibody analysis was negative.

In February 2025, the bronchoscopy with bronchoalveolar lavage (BAL) was performed as part of the diagnostic workup. Microbiological examination identified *Streptococcus mitis* at a concentration of 10^5 CFU/mL, which was considered consistent with oral flora contamination rather than a clinically significant pathogen. Although the lung biopsy was considered for definitive diagnosis, the patient declined the procedure.

Given the absence of evidence supporting an infectious etiology, systemic corticosteroid therapy was initiated in February 2025. On day 1, methylprednisolone 24 mg daily (approximately 0.5 mg/kg based on ideal body weight) was started, together with trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jirovecii* infection.

Within one week, the patient experienced substantial clinical improvement. Follow-up CT performed four weeks after treatment initiation demonstrated near-complete resolution of the bilateral pulmonary infiltrates, with only minimal residual ground-glass opacities remaining (Figure *1B*).

Methylprednisolone 24 mg daily was maintained for four weeks and subsequently tapered by 4 mg every seven days.

In April 2025 (day 65 of steroid treatment), while receiving methylprednisolone 8 mg daily, the patient developed recurrent dyspnea, cough, weakness, and exercise intolerance. Vital signs revealed a respiratory rate of 23 breaths/min, a heart rate of 91 beats/min, and an oxygen saturation (SpO_2) of 93% on room air, which further decreased to 89%-90% following ambulation. A repeat CT demonstrated recurrent bilateral ground-glass opacities and consolidative infiltrates, compatible with relapsed organizing pneumonia (Figure *2A*).

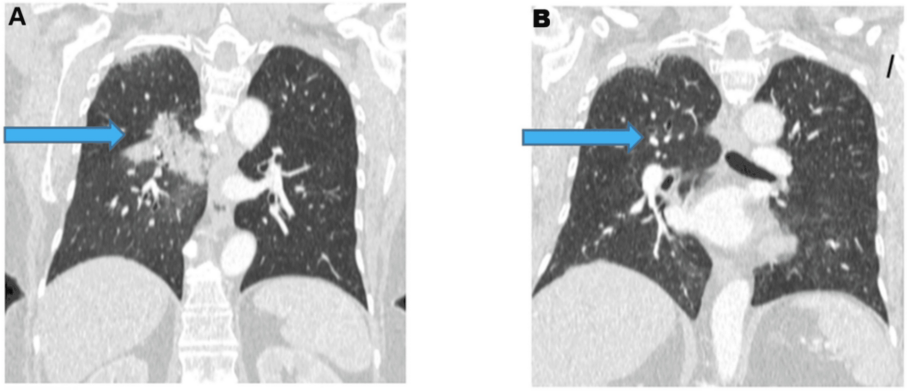


FIGURE 2: Comparison of recurrent pulmonary infiltrates and radiological response after corticosteroid re-escalation.

(A) CT image obtained during clinical relapse showing recurrent consolidative and ground-glass pulmonary opacities in the right lung. (B) Follow-up CT demonstrating near-complete resolution of the previously observed abnormalities following re-escalation of methylprednisolone therapy, with only minimal residual parenchymal changes remaining.

Following multidisciplinary team discussion, methylprednisolone was reinitiated in April 2025, at 12 mg daily, which was considered the minimum effective maintenance dose. Clinical symptoms again resolved within one week. After four weeks of treatment, gradual tapering was reattempted using the same schedule. In May 2025 (after one month of steroid treatment), there was a complete radiological resolution of the pulmonary abnormalities, with only faint residual post-inflammatory changes remaining in the previously affected regions (Figure *2B*).

Two months after complete radiological resolution of the pulmonary abnormalities on CT, and following a one-month steroid-free period, the patient again presented with dry cough, dyspnea on exertion, and fatigue. Repeat CT demonstrated recurrent bilateral ground-glass opacities and consolidative infiltrates, more prominent in the left lung (Figure *3A*).

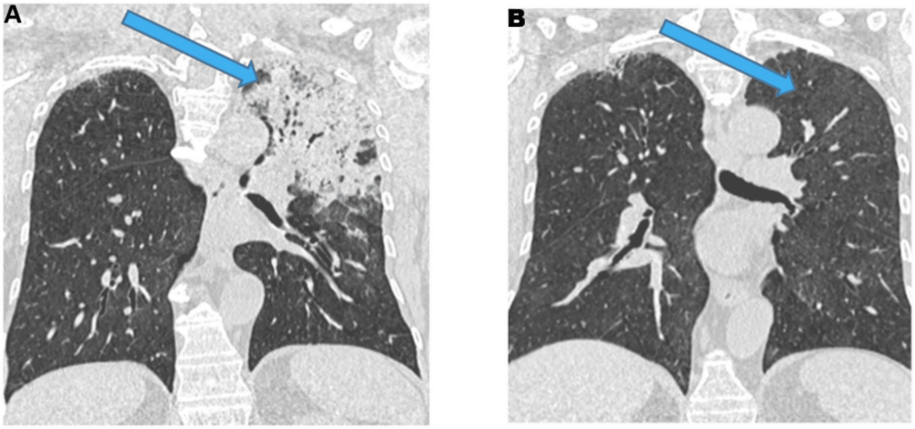


FIGURE 3: Radiological findings during recurrence and after treatment modification.

(A) Coronal chest CT obtained during the second relapse demonstrating extensive consolidative and ground-glass opacities predominantly involving the left upper and mid lung, consistent with recurrent organizing pneumonia. (B) Follow-up coronal chest CT performed after re-initiation of methylprednisolone therapy and discontinuation of letrozole, demonstrating complete resolution of the previously identified pulmonary infiltrates. Residual findings were limited to post-radiation fibrotic changes within the right lung.

Following multidisciplinary review and targeted literature evaluation, letrozole-associated organizing pneumonia was considered a potential explanation for the recurrent pulmonary findings. Consequently, letrozole therapy was discontinued. The patient remained on methylprednisolone 18 mg daily for one month, followed by gradual tapering. The corticosteroid treatment course was completed in July 2025.

A follow-up CT scan performed in three months demonstrated complete resolution of the previously identified pulmonary infiltrates, with only residual post-radiation fibrotic changes in the right lung remaining (Figure *3B*). Following successful corticosteroid discontinuation and multidisciplinary reassessment, endocrine therapy was resumed with tamoxifen 20 mg daily.

At the most recent follow-up in October 2026, approximately 15 months after completion of corticosteroid therapy, the patient remained asymptomatic, with no clinical or radiological evidence of recurrent organizing pneumonia.

Discussion

Aromatase inhibitors and rare pulmonary toxicities

Letrozole, a third-generation non-steroidal aromatase inhibitor, is widely used as adjuvant endocrine therapy for hormone receptor-positive breast cancer [8]. Although generally well tolerated, aromatase inhibitors have been associated with a spectrum of adverse events, most commonly musculoskeletal symptoms, vasomotor disturbances, and metabolic abnormalities [9]. Pulmonary toxicities are rare but have been described, including interstitial lung disease and organizing pneumonia [5]. Published reports of letrozole-associated organizing pneumonia remain limited, making this an uncommon but clinically relevant adverse event.

Organizing pneumonia remains a diagnostic challenge because its clinical and radiological manifestations often mimic infectious pneumonia, radiation-induced lung injury, and other inflammatory pulmonary disorders [10]. In the present case, extensive diagnostic evaluation did not identify a convincing infectious etiology. Furthermore, the patient demonstrated repeated clinical and radiological responses to corticosteroid therapy, supporting an inflammatory rather than infectious process.

A notable feature of this case is the recurrent nature of the pulmonary infiltrates. Despite initial improvement with corticosteroid treatment, multiple relapses occurred while letrozole therapy was continued. Following discontinuation of letrozole and re-initiation of corticosteroid therapy, complete radiological resolution was achieved, and no further recurrences were observed during follow-up. Although this observation does not establish causality, it raises the possibility of a contributory role of letrozole in the development or persistence of organizing pneumonia.

Several observations support a possible association between letrozole therapy and organizing pneumonia in this patient. These include the temporal relationship between drug exposure and pulmonary toxicity, exclusion of alternative infectious causes, repeated responsiveness to corticosteroid therapy, recurrence

during continued letrozole treatment, and the absence of further relapses following drug discontinuation. Although rechallenge was not performed and causality cannot be definitively established, the overall clinical course is compatible with a drug-associated pulmonary toxicity.

The mechanisms underlying aromatase inhibitor-associated pulmonary toxicity remain poorly understood [4]. A potential explanation involves immune dysregulation resulting from profound estrogen depletion. Similar inflammatory pulmonary syndromes have been described with other anticancer therapies, particularly immune checkpoint inhibitors [11]. Although the underlying biological mechanisms differ substantially, immune-mediated inflammatory injury has been proposed as a common pathway contributing to pulmonary toxicity.

Potential contribution of prior thoracic radiotherapy

The relationship between radiotherapy and organizing pneumonia remains complex. RIOP is a recognized complication of breast irradiation, occurring in approximately 0.8%-2.9% of treated patients [6]. Importantly, RIOP may extend beyond the radiation field and occasionally involve the contralateral lung.

Several previously published cases of organizing pneumonia occurring during aromatase inhibitor therapy have also involved prior or concurrent thoracic radiotherapy [12]. Therefore, distinguishing between radiation-induced and drug-associated organizing pneumonia may be challenging. In our patient, the initial pulmonary abnormalities were predominantly located within previously irradiated lung regions, supporting a potential contribution of prior radiation exposure. However, the bilateral distribution of infiltrates, repeated relapses during continued letrozole therapy, and the absence of further recurrence following letrozole withdrawal suggest that radiation injury alone may not fully explain the clinical course.

Rather than representing mutually exclusive mechanisms, prior thoracic irradiation and letrozole exposure may have acted as complementary factors contributing to pulmonary inflammation. Previous radiation-induced tissue injury could potentially create a vulnerable inflammatory microenvironment, thereby increasing susceptibility to subsequent drug-associated lung toxicity. Although this hypothesis cannot be confirmed by a single case report, it may explain the clinical pattern observed in our patient and warrants further investigation.

Estrogen and its role in inflammation

Estrogen receptors are widely distributed throughout the human body, including the lung parenchyma, where the ER-β subtype is expressed [13]. Experimental studies suggest that ER-β signaling may contribute to the regulation of pulmonary immune responses through modulation of inflammatory pathways, including NF-κB-mediated cytokine production [14]. Aromatase inhibitors reduce systemic estrogen levels and may therefore influence these regulatory mechanisms [15].

Although direct evidence linking estrogen depletion to organizing pneumonia remains limited, disruption of local immune homeostasis represents one potential explanation for the inflammatory pulmonary toxicity observed in rare cases of aromatase inhibitor therapy. Additional research is needed to better understand the biological mechanisms underlying these uncommon adverse events.

Limitations

Several limitations should be acknowledged. Histopathological confirmation was not obtained because the patient declined lung biopsy, and therefore, the diagnosis was based on clinical presentation, radiological findings, exclusion of alternative etiologies, and response to treatment. Furthermore, corticosteroid therapy was reinitiated simultaneously with discontinuation of letrozole during the final relapse. Consequently, the relative contribution of each intervention to the observed clinical and radiological improvement cannot be determined with certainty.

Conclusions

This case describes recurrent organizing pneumonia occurring during adjuvant letrozole therapy in a patient previously treated with locoregional radiotherapy for breast cancer. Although causality cannot be definitively established, the clinical course was notable for repeated relapses despite corticosteroid responsiveness while letrozole therapy was continued, followed by sustained clinical and radiological remission after letrozole discontinuation. These observations suggest a possible association between letrozole therapy and the development or persistence of organizing pneumonia. The coexistence of prior thoracic irradiation and aromatase inhibitor treatment raises the possibility that radiation-induced lung injury may increase susceptibility to subsequent inflammatory pulmonary complications. While radiation-induced organizing pneumonia remains an important alternative explanation, the recurrent pattern observed during ongoing letrozole exposure suggests that both factors may have contributed to the clinical presentation.

This case highlights the importance of considering aromatase inhibitor-associated organizing pneumonia in

breast cancer survivors presenting with recurrent pulmonary infiltrates, particularly when infectious and malignant etiologies have been excluded. Early recognition, multidisciplinary evaluation, and timely modification of therapy may facilitate diagnosis, prevent unnecessary interventions, and improve patient outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Salome Kordzaia, Lasha Khmaladze, David Tabagari

Disclosures

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References

1. Menon G, Alkabban FM, Ferguson T: Breast cancer. StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL); 2024.
2. Breastcancer.org. Molecular subtypes of breast cancer. (2024). https://www.breastcancer.org/types/molecular-subtypes.
3. Burstein HJ, Lacchetti C, Anderson H, et al.: Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2019, 37:423-38. 10.1200/JCO.18.01160
4. Khaled A, Mezeraany C, Zanze T, Alila I, Regaieg K: Letrozole-induced pneumonitis complicated by acute respiratory distress syndrome: a case report. Cureus. 2026, 18:e108734. 10.7759/cureus.108734
5. Picado C, Soler N: Organizing pneumonia caused by letrozole therapy for breast cancer: a case report. Arch Bronconeumol. 2025, 61:319-20. 10.1016/j.arbres.2025.01.016
6. Kohilakis E, Pennock M, Tang J, et al.: Radiation-induced organizing pneumonia after hypofractionated whole breast radiotherapy for breast cancer. Ann Breast Cancer. 2024, 7:1028.
7. Khusainova E, Stover DE: Organizing pneumonia—review of clinical and radiographic findings, treatment and outcomes. Lung Pulm Respir Res J. 2022, 3:121.
8. Dumas E, Hamy AS, Wanis KN, et al.: Outcomes of anastrozole, letrozole, and exemestane in patients with postmenopausal breast cancer. JAMA Netw Open. 2025, 8:e2550842. 10.1001/jamanetworkopen.2025.50842
9. Nardin S, Ruffilli B, Landolfo TL, et al.: Aromatase inhibitors as adjuvant therapy in early breast cancer: insights into toxicities and their management. Cancers (Basel). 2025, 17:2726. 10.3390/cancers17172726
10. Lazor R: Organizing pneumonias. Orphan Lung Diseases. 2014, 11:363-78.
11. Li C, Faiz SA, Boysen-Osborn M, Sheshadri A, Wattana MK: Immune checkpoint inhibitor-associated pneumonitis: a narrative review. West J Emerg Med. 2025, 26:210-8. 10.5811/westjem.20305
12. Alati A, Pierre C, Leobon S: Bronchiolitis obliterans organizing pneumonia after breast cancer radiotherapy and letrozole: a case report and literature review. Arch Med Case Rep Case Study. 2021, 4: 10.31579/2694-0248/049
13. Chen P, Li B, Ou-Yang L: Role of estrogen receptors in health and disease. Front Endocrinol. 2022, 18:839005. 10.3389/fendo.2022.839005
14. Ekpruke CD, Silveyra P: The role of estrogen receptors in lung diseases. Am J Physiol Lung Cell Mol Physiol. 2026, 330:L159-68. 10.1152/ajplung.00060.2025
15. Aeffner F, Traylor ZP, Yu EN, Davis IC: Double-stranded RNA induces similar pulmonary dysfunction to respiratory syncytial virus in BALB/c mice. Am J Physiol Lung Cell Mol Physiol. 2011, 301:L99-L109.

10.1152/ajplung.00398.2010