



Case Report

Paclitaxel-induced acute fibrinous and organizing pneumonitis in early breast cancer: A case report

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ABSTRACT

Background: Paclitaxel is a chemotherapeutic drug widely used in breast cancer treatment. While common side effects are possible, paclitaxel-induced pneumonitis is rare, with an estimated incidence of 1%–5% and a high mortality rate.

Case presentation: A 57-year-old Thai woman diagnosed with stage II right breast cancer. She received adjuvant chemotherapy comprising doxorubicin and cyclophosphamide, followed by weekly paclitaxel. After the ninth paclitaxel cycle, she developed acute respiratory failure. Transbronchial biopsies revealed acute fibrinous and organizing pneumonitis. The patient was placed in prone position. Following the administration of dexamethasone, her symptoms improved. However, while reducing the dexamethasone dosage, she developed new-onset dyspnea as well as Takotsubo cardiomyopathy. Intravenous methylprednisolone 500 mg/day was administered for 3 days followed by transition to intravenous dexamethasone and slow tapering to prednisolone. Prednisolone was gradually tapered and eventually discontinued after 3 months. **Conclusions:** Paclitaxel-induced pneumonitis is a rare complication. The diagnosis should be considered in any patient who develops respiratory symptoms while receiving paclitaxel. Acute fibrinous and organizing pneumonitis is a rare type of interstitial pneumonitis with high recurrence and mortality rates. High-dose steroids are needed to treat this type of pneumonitis.

1. Background

Paclitaxel, a chemotherapeutic agent originally derived from the bark of the North American yew tree, *Taxus brevifolia*, has been used primarily in ovarian and breast cancer treatment [1]. Notably, paclitaxel has demonstrated significant activity in various other cancers, including small-cell and non-small-cell lung cancer, head and neck cancers, and gastric cancer [1]. The cellular mechanism of paclitaxel involves inducing mitotic block by stabilizing microtubules, thereby reducing the dynamic nature of these cytoskeletal structures [2].

Common adverse effects of paclitaxel comprise neutropenia, alopecia, peripheral neuropathy, nausea with vomiting, arthralgia, myalgia, and hypersensitivity reactions [3,4]. The latter is triggered by its diluent, polyoxyethylated castor oil, known as Cremophor EL, and the adverse effects can be mitigated through premedication with steroids and histamine receptor antagonists [3,4]. While common side effects are well-known, paclitaxel-induced pneumonitis is rare, cautiously estimated to occur at a rate of 1%–5% [5].

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To the best of our knowledge, our case is the first reported instance of paclitaxel-induced acute fibrinous and organizing pneumonitis (AFOP). In this report, we describe the patient's clinical symptoms, radiographic and computed tomography (CT) findings, and biopsy-confirmed AFOP resulting from paclitaxel administration. This unique case demonstrates the complexity of treatment in drug-induced AFOP, as the symptoms temporarily improved upon steroid administration but deteriorated again upon tapering. The patient provided informed consent.

2. Case presentation

A 57-year-old Thai woman was diagnosed with early-stage right breast cancer in February 2021. Her medical history included hypertension, and she was a non-smoker. On May 3, 2021, she underwent right total mastectomy with sentinel lymph node dissection. Pathology results revealed grade III invasive ductal carcinoma, with the mass measuring 3.1 cm in diameter. Immunohistochemical analysis indicated negative expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, with a Ki67 index of 50%. Sentinel lymph node dissection showed no metastasis in the four dissected lymph nodes. This resulted in a final pathologic stage of pT2N0M0, classified as stage II.

Following the surgery, the patient underwent four cycles of adjuvant chemotherapy with doxorubicin and cyclophosphamide, administered at 3-week intervals. Subsequently, a regimen of weekly paclitaxel at 80 mg/m² over 1 hour was planned for 12 cycles. A standard premedication protocol comprising dexamethasone, chlorpheniramine, and ondansetron was administered prior to the paclitaxel infusion, followed by a 3-day course of dexamethasone at 8 mg per day post-infusion. The patient completed nine cycles of weekly paclitaxel, which was generally well-tolerated, except for the development of grade II peripheral neuropathy after the fourth cycle.

Approximately 1 week after completing the ninth cycle, the patient experienced exertional dyspnea that persisted for 2 weeks with no cough or fever. Her symptoms worsened progressively, prompting her referral to the emergency room on the day scheduled for her tenth cycle of paclitaxel. At this point, her oxygen saturation was 75%–82% on room air, necessitating intubation. Physical examination revealed rhonchi in the right lung. A complete blood count revealed a white blood cell count of $4.7 \times 10^3/\text{mL}$, with 85% neutrophils and no peripheral eosinophilia.

3. CT, computed tomography

A chest radiograph revealed multifocal reticulonodular patchy opacities in both lungs (Fig. 1A). Chest CT demonstrated newly developed multifocal consolidations and ground glass opacities in both lungs. Lesions were distributed along the peribronchovascular regions, suggesting an infectious or inflammatory process. Additionally, several subcentimeter right paratracheal, paraaortic, subcarinal, and bilateral hilar lymph nodes were visible, with diameters measuring up to 0.9 cm. These were considered reactive lymph nodes. Furthermore, concentric intraluminal filling defects were observed in the anterior, medial, and posterior basal segmental branches of the right lower lobar pulmonary arteries, as well as the posterior basal segmental branch of the left lower lobar pulmonary artery, indicative of acute pulmonary embolism (Fig. 1B).

Empirical antibiotic therapy comprising meropenem, levofloxacin, oseltamivir, and trimethoprim-sulfamethoxazole was initiated to address potential bacterial/viral pneumonias and *Pneumocystis carinii* pneumonia. Enoxaparin treatment was also initiated for the acute pulmonary embolism. The patient was placed on a ventilator with the fraction of inspired oxygen set at 1.0. Arterial blood gas analysis indicated a pH of 7.319, partial pressure of carbon dioxide of 36, partial pressure of oxygen of 60.6, and an arterial pO₂(P) from arterial blood gas divided by FIO₂(F) or P/F Ratio was 60.6.

Throughout her hospital stay, the patient remained afebrile, and the scant sputum was clear in color. To ascertain the cause of the pneumonitis, bronchoscopy with bronchoalveolar lavage and transbronchial biopsies were performed the following day. Notably, the results of throat swab real-time polymerase chain reaction (RT-PCR) testing for a panel of 33 viruses, including influenza and severe acute respiratory syndrome coronavirus 2, were negative. Microscopic examination of the bronchoalveolar lavage using Wright's, acid-fast bacilli, and modified acid-fast bacilli stains revealed no identifiable pathogens. Additionally, aerobic bacterial and fungal cultures from the lavage were negative. Further testing, namely PCR for mycobacteria and *Aspergillus* (galactomannan) antigen, with

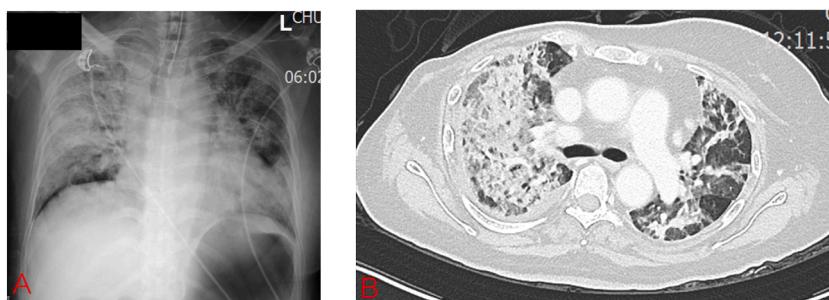


Fig. 1. A: Chest X-ray showing multifocal reticulonodular patchy opacities in both lungs. B: Chest CT chest showing newly developed multifocal consolidations and ground glass opacities involving both lungs, with a peribronchovascular distribution.

an immunofluorescence assay and PCR for *Pneumocystis*, yielded negative results. Hemoculture results were also negative for all specimens.

Transbronchial biopsies revealed alveolar septal thickening, which was attributed to increased fibroblastic stroma and mononuclear inflammatory cells. Notably, frequent interalveolar fibrin leakage was observed, with a varying admixture primarily composed of macrophages, a smaller number of lymphocytes, and occasional neutrophils. Pneumocyte hyperplasia with reactive changes was also evident. Bronchial tissue exhibited mild lymphocyte infiltration with no neutrophil infiltration. No granulomas, foamy material, fungi, or viral inclusions were detected. These pathological observations consistently aligned with moderate subacute lung injury, morphologically congruent with AFOP (Fig. 2).

Following the bronchoscopy, the patient's symptoms worsened, leading to a diagnosis of paclitaxel-induced pneumonitis accompanied by severe acute respiratory distress syndrome. To address the patient's deteriorating condition, the muscle relaxant cisatracurium and the sedative drugs fentanyl and midazolam were administered, and she was placed in the prone position. Intravenous dexamethasone at a dosage of 10 mg every 12 hours was initiated, resulting in observable symptom improvement, as evidenced by a chest X-ray that revealed reduced lung infiltrations compared with the earlier images (Fig. 3A). However, upon reducing the dexamethasone dosage to 8 mg every 12 hours on the 10th day of admission, the patient experienced new-onset dyspnea. A subsequent chest X-ray indicated progression of multifocal reticulonodular patchy infiltrations (Fig. 3B). Concomitantly, she developed tachy-brady arrhythmia and hypotension. The concentrations of the cardiac biomarkers creatine kinase-MB, troponin-T, and N-terminal pro-brain natriuretic peptide were elevated. Echocardiography revealed a left ventricular ejection fraction of 10%–15%, leading to a diagnosis of Takotsubo cardiomyopathy (stress-induced cardiomyopathy). High-dose inotropic drugs, specifically norepinephrine, were introduced to stabilize the hemodynamics. The patient also received a temporary pacemaker to manage the arrhythmia. Intravenous methylprednisolone 500 mg was administered for 3 days, followed by transition to intravenous dexamethasone.

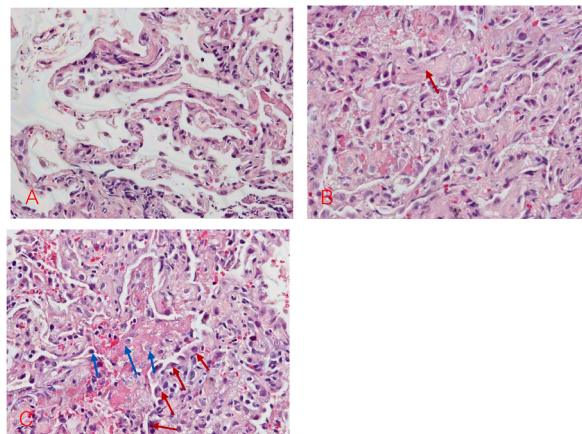


Fig. 2. A and B show the range of alveolar septal thickening from mild to moderate due to increased fibroblastic stroma (red arrow) and mononuclear inflammatory cell infiltration. C shows multiple areas of intra-alveolar fibrin leakage with mononuclear infiltration (blue arrows) and pneumocyte type II hyperplasia with reactive atypia (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

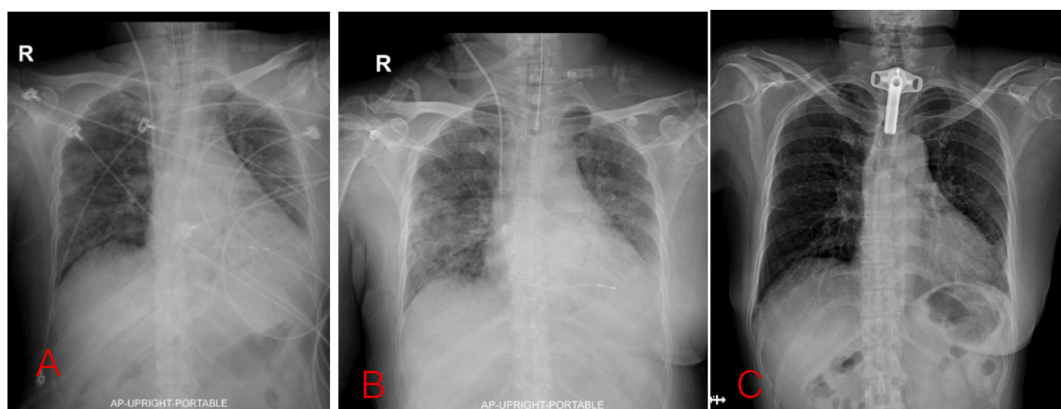


Fig. 3. A: Chest X-ray after dexamethasone administration showing some improvement in the infiltrations. B: Chest X-ray after tapering the dose of dexamethasone showing increased infiltration in both lungs. C: Chest X-ray after slowly tapering the dexamethasone and eventually stopping prednisolone for 4 months showing near-normal findings.

Dexamethasone was continued for 30 days, after which dexamethasone was changed to prednisolone. A tracheostomy was performed owing to the prolonged need for intubation. After 41 days of admission, the patient was successfully weaned from the ventilator.

Considering the severity of the adverse effects, the decision was made to discontinue the paclitaxel. Upon discharge, the patient received prednisolone 0.5 mg/kg/day. Subsequent chest X-ray showed improvement in the previous findings. Follow-up echocardiography before discharge demonstrated an improved left ventricular ejection fraction of 60%. Prednisolone was gradually tapered and eventually discontinued 3 months after discharge. Initially requiring oxygen supplementation at home for 2 months, the patient eventually regained the ability to ambulate without the need for supplemental oxygen. A chest X-ray obtained 4 months after discontinuing prednisolone revealed near-normal lung findings (Fig. 3C).

4. Discussion

Paclitaxel-induced pneumonitis represents a rare yet potentially fatal complication, underscoring the importance of prompt recognition and management. Any patient undergoing paclitaxel treatment who presents with dyspnea and/or fever warrants consideration for this complication, and early investigation through chest imaging is paramount.

The proposed risk factors for paclitaxel-induced pneumonitis are pre-existing pulmonary fibrosis, prior emphysematous changes, concurrent radiation therapy, and combination therapy with other chemotherapy agents [6,7]. Intriguingly, factors such as smoking status, age, and performance status have not demonstrated significant associations with the risk of pneumonitis [6,7]. Notably, the risk of pneumonitis with paclitaxel appears to be linked to dosing schedules rather than the total dose administered. The CALGB 9840 randomized phase III trial comparing weekly and every-3-weeks paclitaxel for metastatic breast cancer revealed that the weekly schedule resulted in a higher occurrence of grade ≥ 3 dyspnea during therapy (7% for weekly vs. 4% for every 3 weeks) [8].

Anoop et al. performed a prospective study in India and reported that among patients who received weekly paclitaxel, 10% developed acute interstitial pneumonitis after one cycle, 5% after two cycles, 3% after three cycles, 8% after five cycles, 3% after seven cycles, 3% after eight cycles, and 3% after twelve cycles [9]. The median number of cycles required to induce interstitial lung disease was five [9].

The precise mechanism underlying paclitaxel-induced pneumonitis remains incompletely understood. Two hypotheses have been postulated: an allergic type (type I hypersensitivity reaction) and a cell-mediated cytotoxic type (type IV hypersensitivity reaction). Type I hypersensitivity reactions involve immunoglobulin E-mediated immune responses and histamine or vasoactive substance release from basophils and mast cells. This hypersensitivity reaction is characterized by acute dyspnea, bronchospasm, hypotension, and an erythematous rash (typically developing shortly after drug administration). This type is observed in up to 30% of cases of paclitaxel-associated adverse reactions, and the rate decreases to 1%–3% with steroid premedication. In contrast, type IV hypersensitivity reactions, also known as delayed-type hypersensitivity, result from T-cell-mediated reactions. Cytokine release activates T-cells or macrophages, leading to tissue damage. Typically, this type manifests as an acute-subacute clinical course over a few hours to 2 weeks and is characterized by bilateral pulmonary infiltrates, resembling the presentation in our case [10,11].

Notably, our case lacked peripheral eosinophilia. Peripheral eosinophilia or neutrophilia is not commonly noted, the presence of hypereosinophilia may indicate a favorable prognosis [12].

The characteristic features observed in our case's chest CT images mirrored those of similar cases, featuring diffuse ground-glass opacities, reticular opacities, thickened septal lines, and irregular airspace consolidations. The findings from the transbronchial biopsy, which revealed interstitial pneumonitis predominantly infiltrated by mononuclear inflammatory cells, lend further support to the proposed hypothesis of a type IV hypersensitivity reaction as the mechanism behind the paclitaxel-induced pneumonitis in our patient.

Of particular interest, the pathological pattern indicated AFOP, which is an infrequent histological presentation of interstitial pneumonitis characterized by intra-alveolar fibrin deposits and widespread organizing pneumonia within alveolar ducts and bronchioles. While this pattern was initially described by Travis in 2002, its etiological spectrum includes connective tissue disorders, drug reactions, occupational exposures, and infections [13,14]. Clinically, this type of interstitial lung disease presents in two patterns: an acute and fulminant course with rapid progression to respiratory failure and death, or a subacute, less fulminating course with eventual recovery. The prognosis is generally grim, marked by a high mortality rate ranging between 50% and 60% [15]. A retrospective study from Japan by Onishi et al. found that AFOP has a high recurrence rate following steroid treatment, ranging between 60% and 76% and necessitating higher corticosteroid doses during recurrences compared with the first episode [16,17].

Diagnosing paclitaxel-induced pneumonitis entails combining clinical and radiological patterns and exposure history, and excluding other causes of diffuse pulmonary infiltration. In our case, the presence of typical clinical, radiological, and pathological findings with the absence of evidence for other infectious agents, led to the diagnosis of paclitaxel-induced pneumonitis.

Corticosteroids remain the cornerstone of paclitaxel-induced pneumonitis treatment. In our case, prompt initiation of dexamethasone led to brief symptom improvement. However, attempting to reduce the steroid dose triggered symptom progression and exacerbation. A similar case has been reported wherein lung oxygenation improved temporarily upon steroid administration but deteriorated again upon tapering [4]. Given the histopathological confirmation of AFOP in our case, and the associated high recurrence rate, we transitioned the patient to pulse methylprednisolone, administering 500 mg/day for 3 days after symptoms worsened. Recommendations for grade 4 (very severe, life-threatening, or disabling) drug-induced interstitial pneumonitis advise pulse methylprednisolone, followed by high-dose steroids (prednisolone 1–2 mg/kg/day) for 2–4 weeks with gradual tapering thereafter [18]. The severity of pulmonary injury dictates the duration of corticosteroid therapy, with our case necessitating a total course of approximately 5 months.

5. Conclusions

- Paclitaxel-induced pneumonitis remains a rare complication of paclitaxel therapy.
- Any patient receiving paclitaxel therapy who exhibits respiratory symptoms accompanied by a diffuse bilateral interstitial pattern should be aware of paclitaxel-induced pneumonitis.
- Prompt administration of steroids is essential upon diagnosis. Since AFOP represents an uncommon subtype of interstitial pneumonitis with high recurrence and mortality rates, high-dose steroids are imperative to effectively manage this variant of pneumonitis.

Ethics approval and consent to participate

This study was meticulously conducted with strict adherence to the ethical principles outlined in the Declaration of Helsinki guidelines governing research involving human subjects. The study protocol underwent thorough review and received approval from the Ethics Committee for Human Research at the Chulabhorn Research Institute (Certificate No.085/2566). Informed consent was provided by the patient.

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Authors' contributions

Data curation, Conceptualization, original draft; and Writing - review & editing, P.L. (Piyarat Limpawittayakul); Supervision, S.P.; Supervision, W.C. and W.B. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors hereby declare that they have no known competing financial interests or personal relationships that could potentially influence the work presented in this manuscript.

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List of abbreviations

| | |
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| CT | Computed tomography |
| RT-PCR | Real-time polymerase chain reaction |
| AFOP | Acute fibrinous and organizing pneumonitis |

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