

[ CASE REPORT ]

## *Pneumocystis jirovecii* Pneumonia in a Patient with Breast Cancer Receiving Neoadjuvant Dose-dense Chemotherapy

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### Abstract:

We herein report a 38-year-old woman with breast cancer who developed *Pneumocystis jirovecii* pneumonia (PCP) during neoadjuvant dose-dense chemotherapy combined with dexamethasone as antiemetic therapy. Chest computed tomography showed bilateral ground-glass opacities and consolidation. The serum  $\beta$ -D-glucan levels were elevated, and *P. jirovecii* DNA was detected from the bronchoalveolar lavage fluid by polymerase chain reaction. Her clinical findings improved with trimethoprim/sulfamethoxazole and adjunctive steroid therapy. Clinicians must be mindful of the manifestations of PCP in non-human immunodeficiency virus (HIV)-infected immunocompromised patients and include the possibility of PCP in the differential diagnosis when confronted with breast cancer on dose-dense chemotherapy showing diffuse lung disease.

**Key words:** chest CT, dexamethasone,  $\beta$ -D-glucan, bronchoalveolar lavage, drug-induced pneumonitis

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### Introduction

*Pneumocystis jirovecii* pneumonia (PCP) is a potentially life-threatening fungal infection in immunocompromised individuals (1). Recently, its incidence has been increasing in patients not infected with human immunodeficiency virus (HIV). The typical chest computed tomography (CT) findings of PCP are symmetric, upper lobe-predominant ground-glass opacities with peripheral sparing (2, 3); however, other less common manifestations are more frequently seen in non-HIV-infected patients, such as consolidation, architectural distortion, and nodules (2, 3). These CT findings are non-specific, and differential diagnoses may include drug-induced pneumonitis, underlying disease involving the lungs, pulmonary haemorrhaging, or other opportunistic infections.

We herein report a case of PCP in a patient undergoing neoadjuvant dose-dense adriamycin/cyclophosphamide (AC) chemotherapy for breast cancer whose clinical findings resembled those of drug-induced pneumonitis.

### Case Report

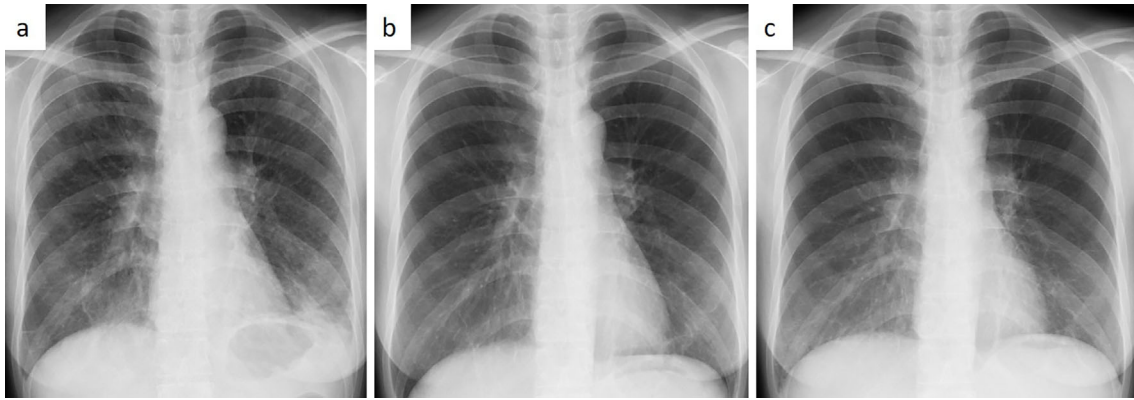
A 38-year-old woman was admitted to our hospital because of a 3-day history of a fever and dyspnoea. She had been previously diagnosed with stage IIB breast cancer. She had been treated with a neoadjuvant dose-dense regimen of chemotherapy consisting of dexamethasone 12 mg, adriamycin 60 mg/m<sup>2</sup>, and cyclophosphamide 600 mg/m<sup>2</sup> on day 1, pegfilgrastim on day 2, and dexamethasone 4 mg on days 2-4. The cycle repeated every two weeks. She received 4 courses of treatment, and the total doses of dexamethasone was 96 mg. After the treatment, she received docetaxel (70 mg/m<sup>2</sup> every 3 weeks), which had been initiated 7 days prior to her presentation at the hospital - the patient reported that the low-grade fever and dyspnoea on exertion had begun 4 days after the start of docetaxel.

The patient was a never-smoker. At presentation, she appeared ill, and her vital signs were as follows: body temperature 37.8°C, blood pressure 99/66 mmHg, heart rate 110

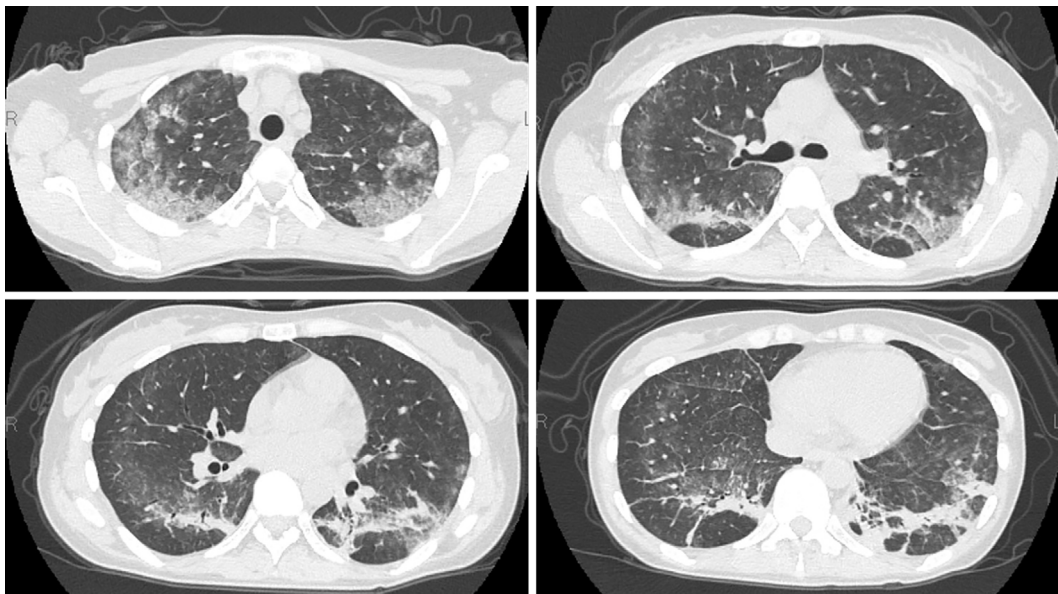
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**Figure 1.** (a) Chest X-ray findings on admission, showing bilateral diffuse infiltration predominantly in the lower lobes. (b) Chest X-ray findings after treatment with methylprednisolone (1,000 mg per day for 3 days), showing marked resolution of infiltration shadows. (c) Chest X-ray findings 4 days after switching to oral prednisolone, showing slightly worsening infiltration in the right lower lobes.



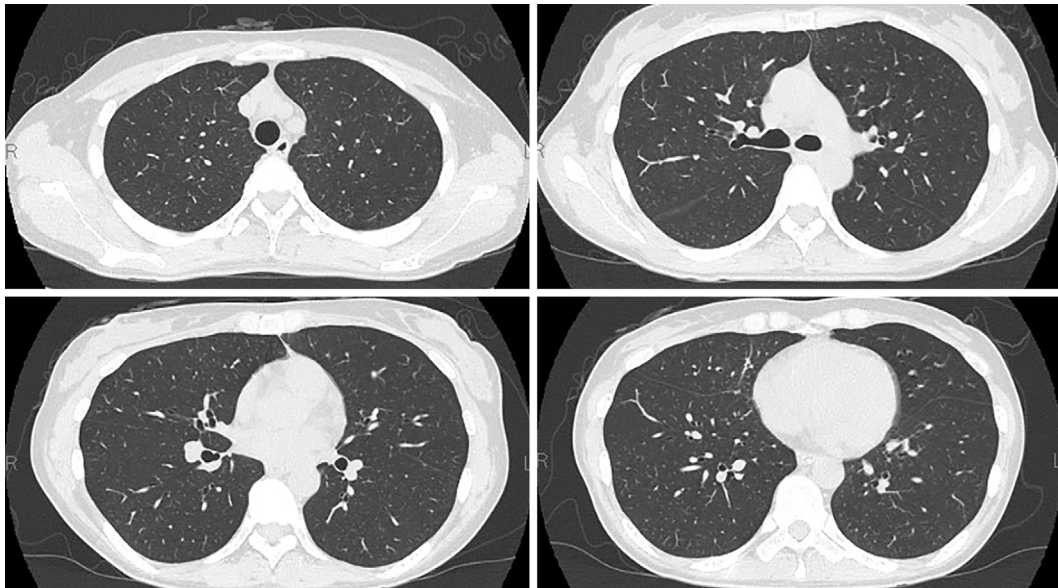
**Figure 2.** Chest computed tomography images on admission, showing bilateral diffuse ground-glass opacities and consolidation with transverse parenchymal bands, which cross the broncho-vascular bundle.

beats/min, respiratory rate 20 breaths/min, and O<sub>2</sub> saturation (SpO<sub>2</sub>) 90% in room air. Fine crackles were audible on both of her lungs. Laboratory examinations showed the following: partial pressure of oxygen (PaO<sub>2</sub>) 57.8 torr on room air, white blood cell count 27,500 cells/mm<sup>3</sup> (80.0% neutrophils, 2.0% lymphocytes), and C-reactive protein (CRP) 13.8 mg/dL. Krebs von den Lungen (KL)-6 and brain natriuretic peptide levels were within the normal range (402 U/mL and <5.8 pg/mL, respectively). The serum β-D-glucan level was found to be slightly elevated (48.5 pg/mL) on the second hospital day. HIV antibody was negative, as were serum *Candida*, *Aspergillus*, and cytomegalovirus antigens.

Chest X-ray showed bilateral diffuse infiltration, and chest CT revealed bilateral ground-glass opacities and airspace

consolidation (Fig. 1a, 2). On the first hospital day, bronchoalveolar lavage (BAL) was performed. An analysis of the BAL fluid (BALF) revealed a total cell count of 2.75×10<sup>5</sup>/mL (lymphocytes 41.7%, neutrophils 16.0%, eosinophils 0.3%) with no malignant cells or pathogenic organisms detected.

Based on these findings, the patient received systemic corticosteroid therapy with intravenous methylprednisolone (1,000 mg/day for 3 days) followed by oral prednisolone at 0.5 mg/kg/day (25 mg/day) under a presumptive diagnosis of drug-induced pneumonitis. After methylprednisolone was started, her symptoms, SpO<sub>2</sub>, and chest X-ray findings improved (Fig. 1b), and her CRP decreased to 2.56 mg/dL. However, on day 4 of oral prednisolone, she again devel-



**Figure 3.** Chest computed tomography findings after treatment with trimethoprim/sulfamethoxazole and a steroid, showing the marked resolution of ground-glass opacities and consolidation.

oped a fever up to 39.3°C. At this time, her CRP level was elevated (6.32 mg/dL), and the chest X-ray findings were slightly worse than before (Fig. 1c). The serum  $\beta$ -D-glucan level was 47.5 pg/mL. SpO<sub>2</sub> was reduced from 98% to 95% on room air. On day 7 of her admission, polymerase chain reaction (PCR) of her earlier BALF specimen was positive for *P. jirovecii* DNA. Lymphocyte stimulation tests (LSTs) with peripheral blood for docetaxel, adriamycin, and cyclophosphamide and with BALF for docetaxel were all negative. Based on these new findings, we diagnosed her with PCP and prescribed trimethoprim /sulfamethoxazole (TMP/SMX, 15 mg/kg/day).

The steroid dose was increased to 60 mg/day because of her respiratory failure on admission. Treatment with TMP/SMX continued for 12 days, during which the patient's clinical symptoms and chest CT findings improved (Fig. 3) and the serum  $\beta$ -D-glucan level decreased to 8.96 pg/mL. Prednisolone was gradually tapered off over two months. Because of adverse events with TMP/SMX, PCP prophylaxis was initiated with atovaquone and continued until prednisolone cessation. After treatment of PCP, total mastectomy for breast cancer was performed.

## Discussion

A definite diagnosis of PCP can be difficult in non-HIV-infected patients. *P. jirovecii* does not grow *in vitro*; therefore, the definite diagnosis of PCP generally relies on the visualization of cysts or trophic forms in respiratory samples by microscopy, using various stains and immunofluorescence methods (1, 4); however, a microscopy-based diagnosis is difficult in non-HIV-infected patients (1, 4), in whom the fungal burden is low (5). PCR can detect very low levels of *Pneumocystis* DNA, but it cannot distinguish PCP from asymptomatic *Pneumocystis* colonization (4).  $\beta$ -D-glucan is

derived from the cell wall of several fungi, including *P. jirovecii*, and has been reported to be useful in the diagnosis of PCP (4, 6). In our case, PCR of the BALF was positive for *P. jirovecii*, and serum  $\beta$ -D-glucan levels were elevated. Furthermore, the patient's clinical symptoms and laboratory and imaging findings improved following treatment with TMP/SMX and adjunctive steroid therapy. These clinical findings and outcomes are consistent with PCP and support our diagnosis of PCP.

Non-HIV-infected immunocompromised patients are at risk for the development of PCP, but estimated incidence rates of PCP have been reported to be low in solid tumours, including breast cancer (7). However, the use of corticosteroids in chemotherapy regimens has been consistently reported as a major risk factor (8). Recently, there have been isolated reports of PCP in patients on dose-dense AC chemotherapy for early breast cancer (9-11). In the dose-dense AC regimen, these agents are administered on an every-two-weeks schedule, while in the standard AC regimen, they are administered on an every-three-weeks schedule. The authors speculated that the dose-dense regimen and dose/time threshold anti-emetic corticosteroids contributed to the development of PCP in their patients (9-11). The majority of patients received 4 cycles of this regimen, and the median time from the start of chemotherapy to the PCP diagnosis was 64 days. The average dose of corticosteroids was 16 mg prednisone equivalent/day over the course of their approximately 56-day-long AC chemotherapy course (9). Our patient had also received 4 courses of this regimen with 11 mg prednisolone equivalent/day prior to the diagnosis of PCP. The time from the start of chemotherapy to the diagnosis of PCP was 65 days, which was similar to the median time previously reported (9-11). Because this infection was not observed in patients receiving a standard cumulative steroid dose over 12 weeks in a non-dose-dense AC regimen, as

Waks mentioned (9), we speculate that the anti-emetic steroid dose/time threshold in the dose-dense AC regimen was linked to the development of PCP in our case.

*P. jirovecii* interacts with lung epithelial cells and immune cells in the lower respiratory tract, resulting in inflammation and causing significant respiratory impairment (1). Corticosteroids exert an anti-inflammatory effect, and there are some reports that, in combination with specific anti-*Pneumocystis* therapy, adjunctive corticosteroid therapy may reduce the morbidity and mortality in non-HIV-infected as well as in HIV-infected patients with PCP (12-14). Although only temporarily, our patient's symptoms and chest X-ray findings improved with steroid treatment before the start of TMP/SMX, likely because of its anti-inflammatory effect. Notably, in our patient, the chest CT findings showed consolidations superimposed on ground-glass opacities, which resembled those of drug-induced pneumonitis (15). As mentioned above,  $\beta$ -D-glucan has been reported to be useful in the diagnosis of PCP, but a uniformly accepted cut-off value has yet to be determined. Based on these findings, as a presumptive diagnosis, we suspected drug-induced pneumonitis over PCP on admission. Furthermore, after the diagnosis of PCP, the steroid dose was increased to 60 mg/day in addition to treatment with TMP/SMX because she had respiratory failure on admission. It is therefore difficult to completely rule out the contribution of drug-induced pneumonitis due to docetaxel, cyclophosphamide, or adriamycin.

A variety of predisposing conditions and drug therapies have been implicated in the development of PCP in non-HIV-infected patients. Accordingly, the risk assessment for PCP may be more complex than was previously thought. Clinicians should be aware that dose-dense AC treatment for breast cancer carries a risk of PCP. Further investigations are needed to clarify whether or not reducing corticosteroids used as anti-emetic medication with chemotherapy and providing concomitant PCP prophylaxis helps reduce the risk for this infection-associated complication.

**The authors state that they have no Conflict of Interest (COI).**

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