—Case Reports—

Organizing Pneumonia Associated with *Pneumocystis jirovecii* in a Patient Receiving Dose-Dense Chemotherapy for Breast Cancer: A Case Report

Mio Yagi[1], Toshihiko Yoneto[1,2], Keiko Yanagihara[1], Koji Nagata[3], Satoru Matsuki[4] and Hiroyuki Takei[5]

[1]Department of Breast Surgery and Oncology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[2]Department of Immunoregulation, Institute of Medical Science, Tokyo Medical University, Tokyo, Japan
[3]Department of Diagnostic Pathology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[4]Department of Pulmonary Medicine and Medical Oncology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[5]Department of Breast Surgery and Oncology, Nippon Medical School Hospital, Tokyo, Japan

In patients not infected by HIV, *Pneumocystis jirovecii* pneumonia (PCP) is characterized by rapid disease progression, difficulty in confirming the diagnosis, and poor prognosis. PCP has also been reported in immunocompromised patients receiving chemotherapy, most often for hematologic tumors, although some patients receiving treatment for breast cancer have been affected. Dose-dense chemotherapy (DDC) which is performed with shorter dosing intervals than standard chemotherapy and is now widely used in clinical practice. However, adverse events have been reported, including infections associated with decreased immune status. PCP infection is considerably more challenging to diagnose and treat than bacterial or viral infections. Furthermore, organizing pneumonia (OP), a pulmonary lesion of PCP, is infrequent and requires caution on the part of clinicians, as protozoan infections require different forms of treatment. Although we initially suspected bacterial, viral, and drug-induced pneumonia in our patient and started treatment with antibiotics, antifungals, and prednisolone, the final diagnosis was OP. The pulmonary lesion of PCP was treated with systemic corticosteroids, leading to recovery. There have been no similar reports of PCP during chemotherapy for malignant disease; however, the possibility of OP should be considered during chemotherapy. Herein, we report a case of PCP during preoperative DDC for advanced breast cancer. (J Nippon Med Sch 2024; 91: 567–573)

Key words: breast cancer, *Pneumocystis jirovecii* pneumonia, organizing pneumonia, dose-dense chemotherapy

Introduction

Pneumocystis jirovecii pneumonia (PCP) is an infectious disease caused by protozoa. It is an opportunistic infection that occurs when the immune system is compromised[1]. PCP has also been reported in immunocompromised patients receiving chemotherapy. Although most often associated with treatment of hematologic tumors[2], PCP has been reported in patients receiving treatment for solid malignant tumors[3,4].

The efficacy of dose-dense chemotherapy (DDC), which is performed with shorter dosing intervals than standard chemotherapy for advanced breast cancer, has been recently confirmed in clinical trials[5,6] and a meta-analysis[7] and is now widely performed, in accordance with the Gompertzian tumor growth model[8]. However, adverse events of DDC have been reported[9], including drug-induced lung damage and infections associated with decreased immune status. In cases of adverse respiratory events such as interstitial lung disease (ILD)[10] and drug-induced pneumonia[11], infectious pneumonia is associated with high mortality. Reliable diagnosis and prompt treatment are therefore important. Protozoan infections

Correspondence to Mio Yagi, Department of Breast Surgery and Oncology, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: m-yagi@nms.ac.jp
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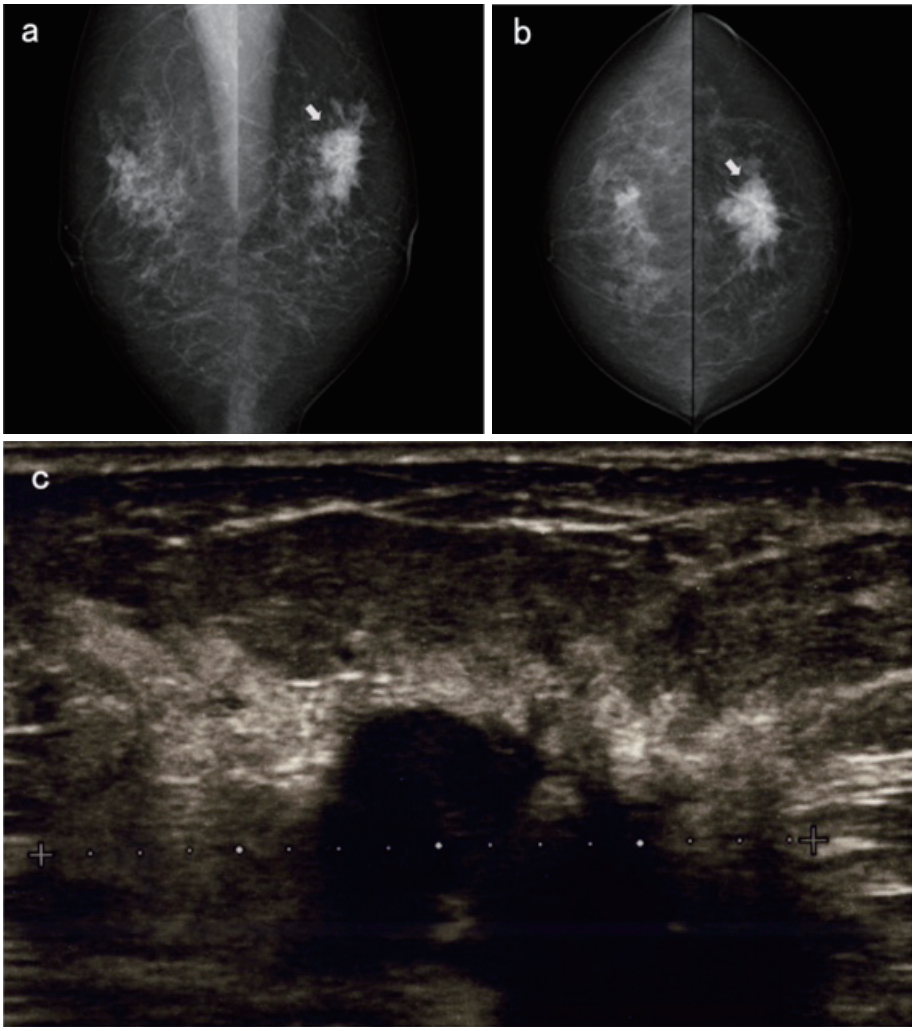

Fig. 1
Mediolateral oblique (a) and craniocaudal (b) mammograms show an irregular hyperdense mass in the left upper outer quadrant (indicated by arrows).
Left breast ultrasound shows an irregularly shaped, hypoechoic solid mass (c).

are more challenging to diagnose and treat than bacterial and viral infections, as cell-mediated immunity is more strongly involved than in viral infections[12]. Prompt diagnosis of PCP is therefore especially important during infectious disease outbreaks. Furthermore, the incidence of PCP due to adverse events from steroid administration has been reported to be 0.6% during dose-dense adriamycin/cyclophosphamide (AC) chemotherapy, as compared with 0% for standard AC chemotherapy[13]. The mortality rate for PCP infection in patients not infected by HIV is very high: 30% to 60%[14]. In addition, although extremely rare, organizing pneumonia (OP) associated with protozoan infection has been reported[15], and it is thus important to consider possible side effects, including OP, during chemotherapy.

Case Presentation

A 72-year-old woman with a lump in her left breast presented to our hospital in July 20XX. Physical examination revealed a mass in the left upper mammary gland, and one enlarged ipsilateral axillary lymph node was identified by palpation. The patient's past medical history and family history were not recorded. Blood examination, including values for tumor markers and HIV antibodies, revealed no abnormalities. Mammography and ultrasound imaging showed an irregular, suspected malignant mass, approximately 38 mm in diameter, in the left upper mammary gland (**Fig. 1a, b, c**). A core needle biopsy revealed invasive ductal carcinoma. Immunostaining results were estrogen receptor-positive (>90%), progesterone receptor-positive (>90%), and human epidermal growth factor receptor 2 expression-negative. The Ki-67 level was 50.9%. Initial whole-body computed tomogra-

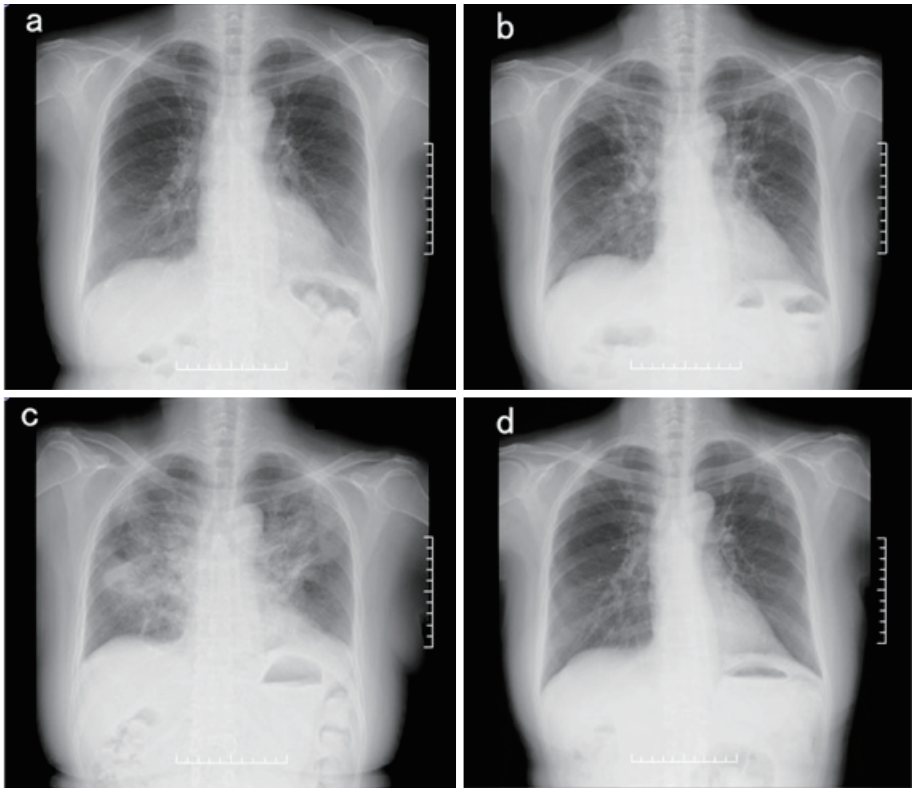

Fig. 2
Chest X-rays show no abnormalities at the end of the 3rd DDC (a); the bilateral apical ground glass changed predominantly in the upper zones at 8 days after the start of the 4th DDC (b); worsening bilateral upper and lower lobe airspace shadowing, and diffuse ground-glass opacity were observed on admission, and after consolidation on the third day, respectively (c), but the latter had completely resolved on day 16 after admission (d).

phy (CT) scanning showed no evidence of distant metastases. The final diagnosis was advanced breast cancer, cT2N1M0 stage IIB, and treatment with neoadjuvant DDC was selected.

From July 20XX, DDC was initiated as follows: dexamethasone 6.6 mg, epirubicin 90 mg/m^2, and cyclophosphamide 600 mg/m^2 on day 1; aprepitant on days 1-3; dexamethasone 8 mg on days 2-3; olanzapine 5 mg on days 1-5 for preventing nausea; and pegfilgrastim for prevention of bone marrow suppression. At the end of the second DDC, the patient had slight breathlessness, but blood examination results were within normal limits.

At the end of the third DDC, the patient developed a fever of 37.2°C and occasional dry cough, but blood examination and a chest X-ray showed no abnormalities (**Fig. 2a**); the fourth course of DDC therefore began as planned. Six days after the start of the fourth DDC, the patient developed a fever of 38.0°C. This was suspected to be the result of an infection of unknown origin, and levofloxacin was administered orally. However, the fever persisted, and a blood examination on the eighth day after the start of DDC revealed a high C-reactive protein level (CRP) of 8.6 mg/dL, and a white blood cell (WBC) count of 4,400/mm^3 (79.0% neutrophils and 12.0% lymphocytes); a chest X-ray showed no abnormalities.

Ten days after the start of the fourth DDC, the patient continued to have a fever of 39.2°C but no dyspnea. Blood examination showed an elevated WBC count of 8,700/mm^3 (71.0% neutrophils and 2.0% lymphocytes) and a CRP level of 12.77 mg/dL. A chest X-ray showed diffuse ground-glass opacity (GGO) in the bilateral upper lobes (**Fig. 2b**), and a chest CT showed diffuse ground alveolar airspace disease in the upper and lower lobes (**Fig. 3a**). The patient was urgently admitted to hospital with suspected ILD, bacterial pneumonia, PCP, and COVID-19 pneumonia. Beginning on the first day of admission, prednisolone (PSL) 60 mg/day, trimethoprim/sulfamethoxazole (TMP/SMX) 720 mg/3,600 mg/day, and cefepime (CMX) 4 g/day were administered. On the third day of admission, the patient's temperature returned to normal, but her respiratory condition continued to worsen. An elevated WBC count of 20,100/μL

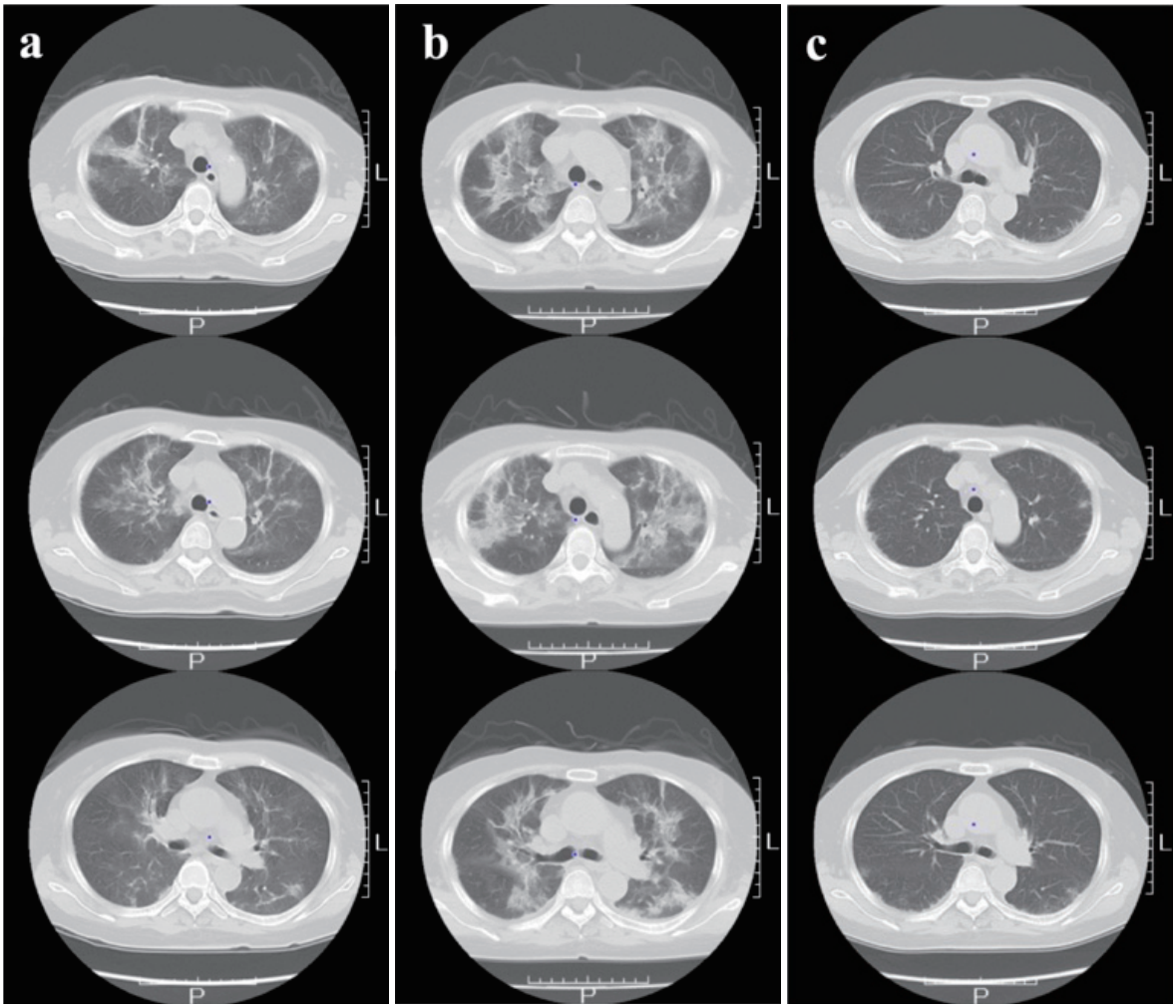

Fig. 3
A chest CT scan at admission shows diffuse ground alveolar airspace disease in the upper lobes 8 days after the start of the 4th DDC (a); widespread ground glass changes with areas of crazy paving were visible on the third day of admission (b), but no abnormalities were observed on day 16 after admission (c).

(90.2% neutrophils and 2.4% lymphocytes) was observed on blood examination, and a chest X-ray and CT scan showed bilateral diffuse GGO and consolidation (**Fig. 2c, 3b**). Nasal swabs and examinations of urine and blood yielded negative results for COVID-19 virus, adenovirus, influenza A and B, legionella antigen, *Streptococcus pneumoniae* antigen, and Mycoplasma. A bacterial blood culture also yielded negative results; however, the results of serum β-D-glucan and Krebs von den Lungen testing were not yet available at this point.

On day 4 of admission, the antibiotic was changed to meropenem hydrate (MEPM), and bronchoalveolar lavage (BAL) was performed. In addition, systemic corticosteroid therapy with intravenous methylprednisolone (mPSL) 1,000 mg/day for 3 days and administration of oral PSL 40 mg/day was initiated for treatment of suspected ILD or OP, a pulmonary lesion of PCP. On day 6 of admission, although the CRP level again increased (to 8.6 mg/dL) and serum β-D-glucan was elevated (116.5 pg/mL), chest X-ray findings showed improvement after administration of mPSL (**Fig. 2d**). PCR examination of the specimen obtained by BAL recognized the deoxyribose nucleic acid from *P. jirovecii* and confirmed a diagnosis of PCP. The patient was then continuously treated with MEPM for 7 days and with TMP/SMX for 21 days. In addition, histopathology of transbronchial lung biopsy showed multiple intra-alveolar granulation tissue buds, known as Masson bodies, and interstitial fibrosis, confirming the diagnosis of OP[16] (**Fig. 4a, b**).

The patient's general condition then improved, as did the results of chest X-rays and CT scans (**Fig. 2d, 3c**). The patient was discharged on day 16 after admission (**Fig. 5**). A subsequent preoperative examination revealed another mass in the contralateral right breast, which was diagnosed as breast cancer, and bilateral total mastectomy were performed. Since then, she has continued to

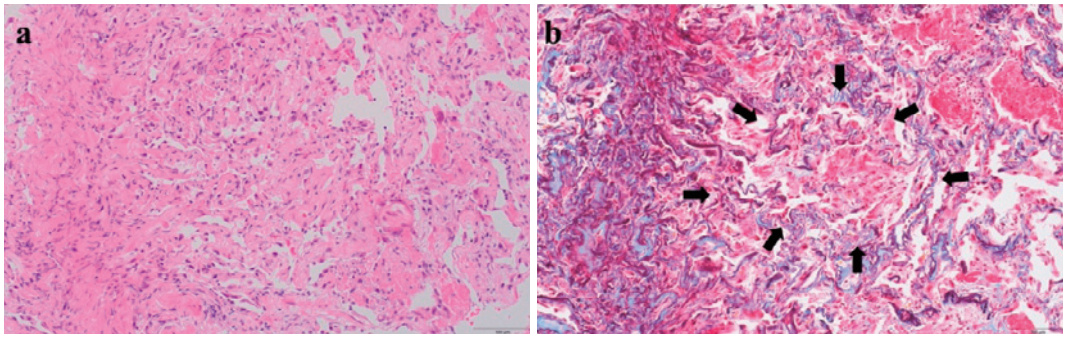

Fig. 4
Hematoxylin and eosin-stained TBLB tissue samples show thickened alveolar septa with mononuclear cell infiltration, plasma cells, fibroblast plug, and histiocytes (a: bar=100 μm).
Elastica-Masson trichrome-stained TBLB tissue samples show that the thickened alveolar septa with lymphocytes, plasma cells and histiocytes, and a fibroblast plug (Masson body: indicated by arrows), consistent with organizing pneumonia (b: bar=100 μm).

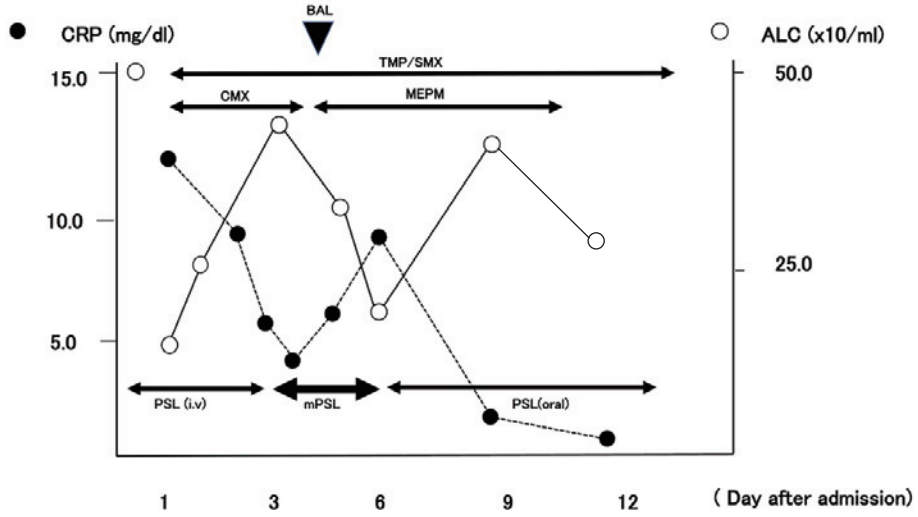

Fig. 5
The graph shows the patient's clinical course from presentation to this writing.

receive hormone therapy as an outpatient.

Discussion

Cases of malignant tumors requiring chemotherapy have been increasing[17,18], as has the incidence of PCP. The mortality rate among PCP patients is as high as 30-60%[19]. However, the scarcity of auscultatory findings and characteristic blood examination findings can complicate diagnosis of PCP, even when patients are severely ill. Elevated serum β-D-glucan has been reported to support the diagnosis[20], but bronchoscopy provides a definitive diagnosis and is thus recommended.

Some evidence indicates that corticosteroid administration during chemotherapy is associated with PCP development in non-HIV patients[4]. In addition, although DDC is currently recommended for advanced breast cancer, the short intervals between steroid doses and the high average daily doses may increase the risk of developing PCP. Patients who developed PCP were treated with a median 16.4 mg prednisone equivalent/day as nausea prophylaxis for a median 64 days[13]. Therefore, PCP should always be considered when chemotherapy is performed.

Although pegfilgrastim has recently been introduced as an insured drug to prevent neutropenia during DDC, it does not prevent lymphocytopenia. In general, cellular immunity is strongly associated with development of PCP, and decreased levels of cluster of differentiation 4 lymphocytes are thought to cause PCP[21]. It has been reported that 90% of patients diagnosed with PCP have a lymphocyte level lower than 1,000 cells/mm^3[3,21], and our patient had lymphopenia. This suggests that DDC prevented recovery of the patient's lymphocyte count before

the next dosing cycle began and may have contributed to PCP onset.

As mentioned above, there are two possible mechanisms by which the risk of PCP may be increased: a decrease in lymphocytes caused by bone marrow suppression by cytotoxic agents and cellular immunosuppression by corticosteroids. To reduce the risk of PCP, several studies have recommended minimizing doses of oral steroids and prophylaxis when the cluster of differentiation 4 count is lower than 300 cells/mm[3,22]. Therefore, lymphocyte counts should be carefully monitored during DDC, and administration of prophylactic antiprotozoal agents should be considered for high-risk patients[23]. For this reason, clinicians should pay more attention to the possibility of PCP.

In the present case, we initially suspected bacterial, viral, and drug-induced pneumonia and started treatment with antibiotics, antifungals, and PSL. However, the final diagnosis was OP, which was treated with systemic corticosteroids, leading to recovery. OP is a nonspecific inflammatory lung disease, generally defined by pathological findings and caused by various factors[24]. Although the primary cause is bacterial infection, viral, parasitic, and fungal infections are also associated with the condition and cannot be treated with antibiotics[24]. It has been reported that a lung biopsy promptly after unsuccessful antibiotic treatment can confirm a diagnosis of OP[25]. A typical histopathological finding in OP is the presence of Masson bodies, which are described as granulation tissue within intra-alveolar buds, which were observed in our patient. OP as a pulmonary lesion of COVID-19 pneumonia[16], as well as OP coinfection with COVID-19 pneumonia and PCP, have been reported[26,27]. An aggressive biopsy and histopathological examination are appropriate when the patient's condition allows. Finally, although there have been no previous reports of OP as a pulmonary lesion of PCP during chemotherapy, our case suggests that this possibility should be considered in the future.

Conflict of Interest: The authors declare no conflicts of interest.

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