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Case Report

Interstitial lung disease with prolonged fever that occurred during long-term administration of olaparib in a 74-year-old ovarian cancer patient: Radiological features and considerations for preventing delayed diagnosis ☆,☆☆

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ABSTRACT

A 74-year-old woman, who had been receiving olaparib for the treatment of ovarian cancer for more than a year, visited the emergency department complaining of a fever that had lasted for 1 month. She had been taking antipyretics and antibiotics for her fever, but without any effect. Although she had no symptoms other than fever, she had stopped taking olaparib for 1 week before her visit because she had developed anemia caused by myelosuppression from olaparib. After discontinuing olaparib, her maximum body temperature decreased. On admission, chest X-ray revealed no abnormalities, but chest CT showed diffuse ground-glass opacities. Chest CT taken 5 days later showed partial improvement; therefore, we diagnosed her with interstitial lung disease (ILD) associated with olaparib. After short-term steroid treatment, the ground-glass opacities disappeared, and the patient became afebrile. The CT scan taken for tumor evaluation 2 days before the onset of fever showed a few centrilobular nodular opacities and small patchy ground-glass opacities. These findings could indicate early lesions of ILD, but they seemed inconspicuous and nonspecific, and it might have been difficult to diagnose ILD then. To date, few cases of ILD associated with ola-

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parib have been reported. However, based on previous reports, fever is often seen, and CT findings mainly comprise diffuse ground-glass opacities, and in some cases, centrilobular nodular shadows. Thus, in conjunction with the findings of the present case, these characteristics may be representative of olaparib-induced ILD.

Introduction

Anticancer agents often cause drug-induced lung injuries, the most common of which is interstitial lung disease (ILD) [1]. There are no specific imaging findings for drug-induced ILD, and it resembles other ILDs, such as idiopathic interstitial pneumonia. Therefore, computed tomography (CT) findings of drug-induced ILD are classified as CT patterns of similar ILDs, for example, organizing pneumonia (OP) pattern, hypersensitivity pneumonia (HP) pattern, nonspecific interstitial pneumonia (NSIP) pattern, etc. [2]. Furthermore, the symptoms of drug-induced ILD are usually nonspecific, such as coughing, dyspnea, and fever, which may occur singly or in combination; these symptoms are also common in other lung diseases. Thus, if drug-induced ILD is not considered, a diagnosis may not be made or may be delayed, even if symptoms and abnormal findings are recorded through an interview and chest imaging is performed.

We present a case of a woman with ovarian cancer who had been receiving the poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib, an oral molecular targeted agent, and experienced drug-induced ILD. This case was diagnosed 1 month after the onset of symptoms and is, therefore, a cautionary case in the diagnosis of drug-induced ILD. The reported incidence of ILD was approximately 1.5% in phase III clinical trials of olaparib maintenance therapy for ovarian cancer [3,4]. However, few cases have been reported, and the characteristics of ILD are not well understood. Therefore, we investigated previous literature and discussed the features of olaparib-induced ILD.

Case presentation

A 74-year-old woman with recurrent ovarian cancer visited the emergency department of our hospital because of a prolonged fever. She had developed a fever of up to 38°C, which lasted for a month. She had no symptoms other than fever. Initially, she was treated with antipyretics and monitored; however, her condition did not improve. Subsequently, it was thought to be an infection; therefore, levofloxacin was administered, but it had no effect. The patient had been receiving olaparib for over 13 months. Continuous use of olaparib caused myelosuppression, and the anemia progressed gradually. A week before her visit, her hemoglobin level dropped to 6.4 g/dL, for which, she received a blood transfusion and olaparib was discontinued. She continued to have a fever after discontinuing olaparib; however, the peak body temperature decreased.

On physical examination, her general condition was good and chest auscultation revealed no abnormalities in the heart or respiratory sounds. Body temperature was 37.3°C, and oxygen saturation was 95%. Blood examination showed a white blood count of 4130/μL, lymphocyte count of 540/μL, hemoglobin level of 8.0 g/dL, platelet count of 83000/μL, and C-reactive protein level of 6.13 mg/dL. Urine examination results were normal. The polymerase chain reaction test did not detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There were no abnormal findings on the chest radiograph (Fig. 1), and a systemic CT scan was performed to investigate the underlying cause of the fever. Chest CT revealed diffuse, faint ground-glass opacities (GGO) in both lung fields (Fig. 2). Because of the myelosuppression, we considered the possibility of an opportunistic infection, such as cytomegalovirus (CMV) pneumonia or *Pneumocystis* pneumonia, but she tested negative for serum CMV antigen and β-d glucan. The serum markers for ILD, including Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D), were elevated to 588 U/mL and 169.0 ng/mL, respectively (normal value: <500 U/mL and <110 ng/mL, respectively). Therefore, the cause of ILD was considered other than infectious disease. Based on the CT findings, HP was considered the most likely ILD. Summer-type HP, caused by the inhalation of *Trichosporon asahii* suspended in the air in houses, is the most common type of HP in Japan; however, she tested negative for the serum antibody for *T. asahii*. Finally, other etiologies of HP were considered, and olaparib was suspected to cause ILD. After admission, she had a low-grade fever; however, the maximum body temperature had decreased, and CT scans taken 5 days later showed that some of the shadows had disappeared (Fig. 3). Thus, the patient was diagnosed with ILD caused by olaparib. ILD was treated with 30 mg/day of prednisolone, and follow-up CT showed that the GGO had completely disappeared 7 days later (Fig. 4). Corticosteroid therapy was administered for a short period.

The patient underwent periodic CT scans to evaluate the status of ovarian cancer. She underwent a CT scan 2 days before the onset of the fever, and we reviewed the CT scan again. Small patchy GGO and poorly defined nodules were detected in both lungs (Fig. 5). These findings did not exist before, and we speculated that they depicted an early lesion of ILD caused by olaparib. The patient was discharged from the hospital and returned home, and the fever did not recur.

Discussion

In the present case, the cause of persistent fever could not be identified early. It is sometimes difficult to identify the ori-

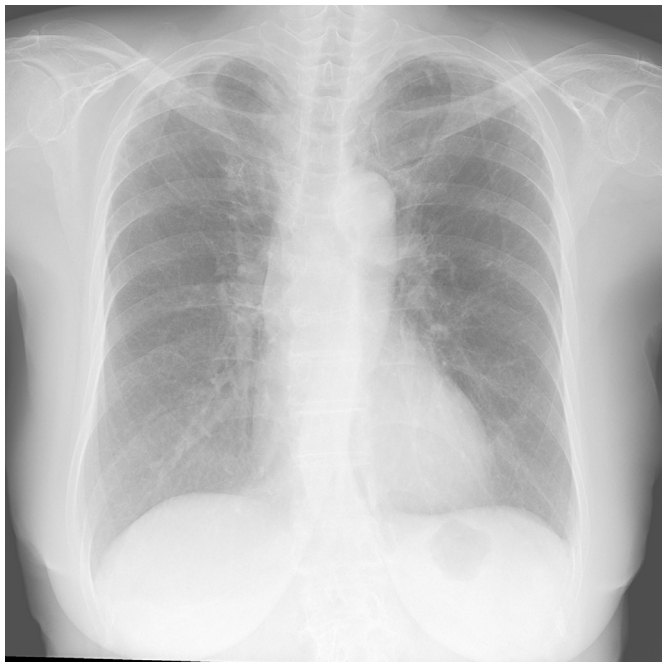

Fig. 1 – Chest X-ray at the diagnosis of ILD. It is difficult to determine the presence of ground-glass opacities.

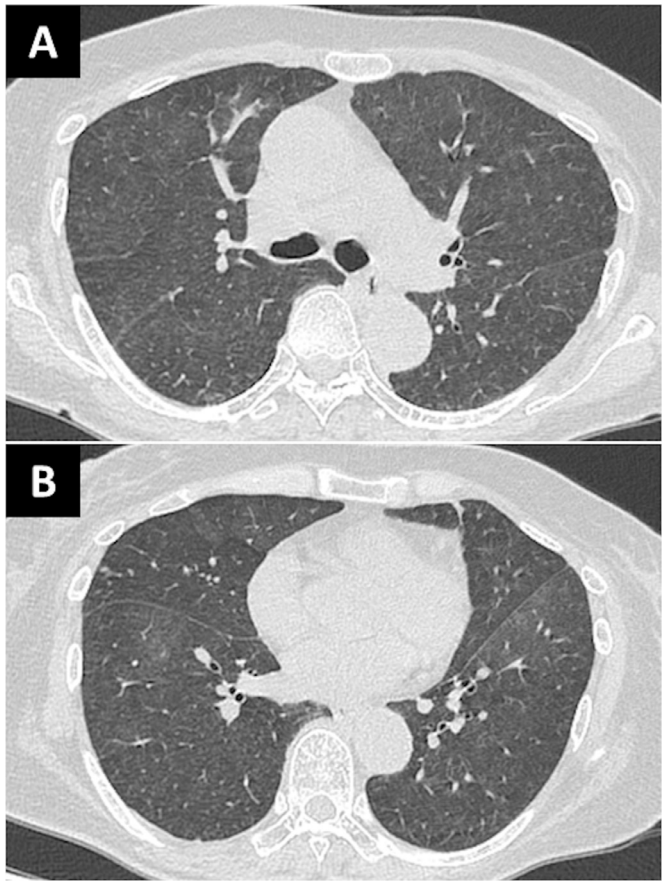

Fig. 2 – (A, B) Chest computed tomography at the emergency department visit. Diffuse faint ground-glass opacities are seen in bilateral lung fields. Ground-glass opacities are defined as a hazy increased attenuation in the lung that does not obscure the pulmonary vascular markings.

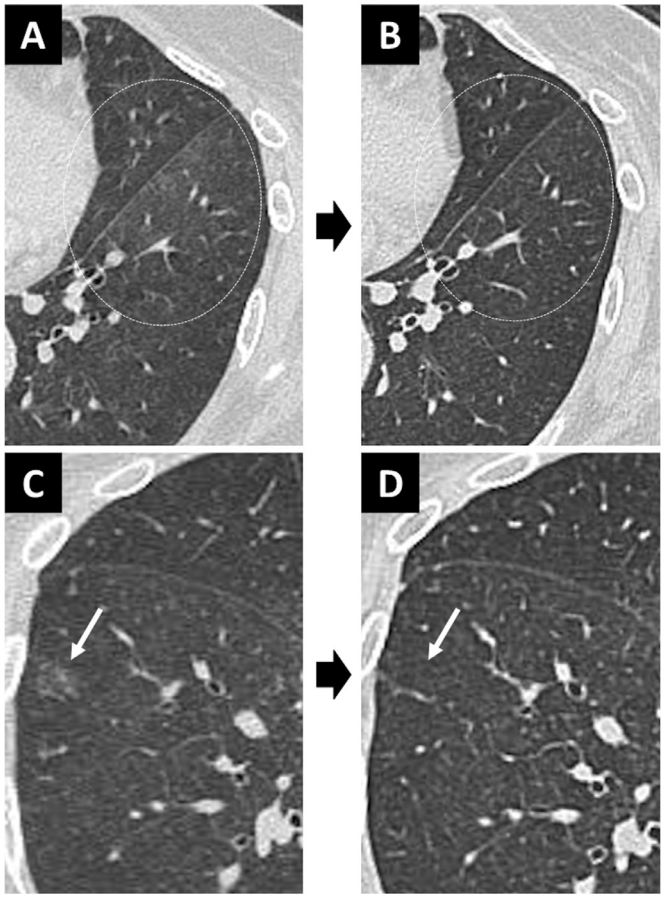

Fig. 3 – Comparison between chest computed tomography at the presentation to the emergency department (A, C) and 5 days later (12 days after discontinuing olaparib) (B, D). The patchy ground-glass opacities (dotted circles) and poorly defined nodular opacities (arrows) disappeared. Poorly defined nodular opacities represent small, rounded pulmonary opacities with ill-defined margins.

gin of fever when the patient presents with only fever and no other symptoms. Generally, drug-induced ILD is diagnosed comprehensively after differential diagnosis of similar diseases. Because this patient had a fever, it was important to differentiate the condition from an infectious disease. Respiratory infection was ruled out because the patient was unresponsive to antibiotics. Blood tests were negative for antigens derived from CMV and PCP, which caused diffuse ground-glass opacities, as in this case. HP caused by environmental factors, such as summer-type HP, was ruled out as there was no recurrence after discharge. After discontinuing only olaparib among the multiple oral medications, the fever tended to decline, and the CT findings also partially improved, making it possible to diagnose olaparib-induced ILD.

There are several reasons for the delayed diagnosis of the present case. First, a long time (more than a year) had passed since the administration of the causative drug till the onset of symptoms. Antineoplastic drugs often cause drug-induced ILD, which usually occurs within a few days to 6 months of starting administration [5]. Therefore, if drug administration is continued safely for an extended period, the risk of developing drug-induced ILD may be underestimated. In a study on PARP inhibitor-related ILD using the FDA Adverse Events Reporting System database, 170 cases of ILD were collected, of which 152 were associated with olaparib [6], with a median onset of ILD of 99 days (interquartile range: 77-241, range: 0-477). Although it is rare for patients to develop ILD even after taking olaparib for more than one year, this case shows that it is necessary to be aware of the development of ILD during treatment. Second, in this case, there were no symptoms other than fever. If the patient had presented respiratory symptoms, the time to diagnosis could have been reduced. However, we should be aware that fever may be the only symptom of ILD. Third, a few poorly defined small nodules and small patchy GGO that appeared to be an initial image of ILD on chest CT taken two days before the onset of fever were inconspicuous and appeared as nonspecific shadows that could not easily be thought of as ILD. If the incidental findings on chest CT at the onset of ILD are insignificant, as in this case, they may be overlooked, and it may be difficult to make an early diagnosis. Careful monitoring is required even if the incidental CT finding is a slightly nonspecific shadow.

Few cases of olaparib-induced ILD have been published, and detailed information, especially regarding the symptoms and CT findings, is not well understood. Table 1 summarizes the information based on previously published case reports

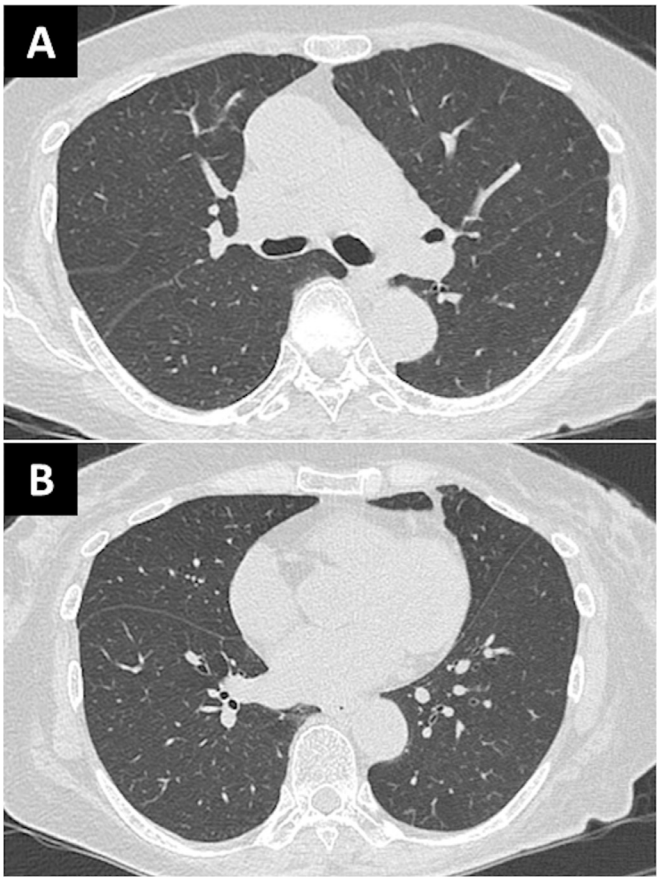

Fig. 4 – (A, B) Follow-up chest CT after corticosteroid treatment for one week. The same region as Fig. 2A and B are presented. A complete disappearance of ground-glass opacities can be seen.

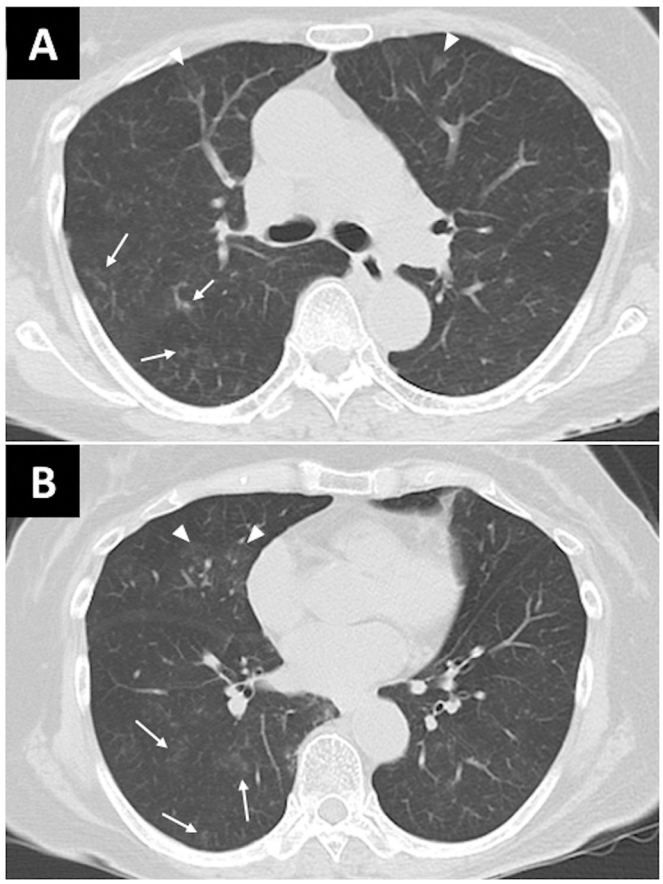

Fig. 5 – (A, B) Chest CT taken two days before the onset of fever. A few small patchy ground-glass opacities (arrowheads) and faint, poorly defined nodular shadows (arrows) are seen.

[7–11] and the present case. Fever was observed in eight of nine cases and is considered a common symptom of olaparib-induced ILD. Regarding chest CT findings, diffuse GGO was the most common shadow. However, notably, 4 of the 9 cases had centrilobular nodular shadows. When the CT findings of these cases are classified into patterns, the most common radiologic pattern is the HP pattern defined as "small, poorly defined centrilobular nodules with or without widespread areas of ground-glass opacity [2]." Fever and HP pattern on chest CT may be characteristic of olaparib-induced ILD. Fur-

Table 1 – Clinical and radiological presentation of previously reported cases of olaparib-induced ILD.

Reference	Number of cases	Time to onset	Symptoms	CT findings	CT pattern
[7]	2	4M	fever, fatigue	Patchy GGO and interlobular septal thickening	NCPE
		2M	fever	Diffuse centrilobular nodules	HP
[8]	1	7W	fever, cough	Diffuse GGO	HP
[9]	1	2M	fever, dyspnea	Diffuse GGO	HP
[10]	1	15W	dyspnea	Diffuse GGO	HP
[11]	3	4M	fever, fatigue	Diffuse faint GGO	HP
		8M	fever, malaise	Diffuse GGO with centrilobular GGN	HP
		3W	fever, dyspnea	Patchy GGO and consolidation with faint centrilobular nodules	NSIP and OP
Present case	1	13M	fever	Centrilobular nodules and patchy GGO followed by diffuse faint GGO	HP

CT, computed tomography; M, months; W, weeks; GGO, ground-glass opacities; GGN, ground-glass nodules; NCPE, noncardiogenic pulmonary edema; HP, hypersensitivity pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

ther case accumulation and research are required to clarify the clinical and radiological features of olaparib-induced ILD.

Conclusion

When patients present with fever while receiving olaparib, differential diagnoses should include drug-induced ILD and infectious diseases. Drug-induced ILD cannot be ruled out even if the patient presents only with a fever. Olaparib-induced ILD mainly manifests as diffuse GGO or HP patterns and is sometimes accompanied by centrilobular nodules. Faint GGO cannot be clearly recognized on chest radiographs; therefore, chest CT is useful for diagnosis. Early recognition and diagnosis of drug-induced ILD improves patient outcomes, and thus, chest CT should be performed immediately when drug-induced ILD is suspected.

Patient consent

Informed consent for the publication of this report was obtained from the patient.

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