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Clinicoradiological course of abemaciclib-induced pneumonitis with histology findings

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SUMMARY

A woman in her late 40s presented with multiple abnormal shadows on high-resolution CT (HRCT), was treated with abemaciclib for recurrent right breast cancer post-surgery and chemoradiation therapy. During the 10-month chemotherapy, HRCT revealed a recurrent pattern of a partly appearing and disappearing organising pneumonia pattern without clinical symptoms. Bronchoalveolar lavage analysis revealed lymphocytosis, while transbronchial lung biopsy revealed alveolitis with epithelial cell injury. Based on the diagnosis of drug-induced pneumonitis due to abemaciclib, the discontinuation of abemaciclib and administration of prednisolone were effective. Abnormal shadow on HRCT disappeared gradually, while elevated Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D levels were restored to normal range. This is the first case report of abemaciclib-induced pneumonitis with histology findings. Since the severity of abemaciclib-induced pneumonitis ranges from mild to fatal, regular monitoring of pneumonitis with radiography, HRCT, and measurement of KL-6 and SP-D levels should be considered.

BACKGROUND

Abemaciclib is a cyclin-dependent kinase 4/6 inhibitor approved for hormone receptor-positive human epidermal growth factor receptor 2-negative metastatic or recurrent breast cancer. In Japan, post-marketing surveillance reported the occurrence of pulmonary toxicity in 82 of 4700 cases and mortality in 13 cases.[1] Thus, the severity of toxicity varies, with few reports of drug-induced pneumonitis due to abemaciclib. We treated a case of abemaciclib-induced pneumonitis with a recurrent pattern of a partly appearing and disappearing ground-glass opacity (GGO) and consolidation. To our knowledge, this is the first report of drug-induced pneumonitis due to abemaciclib supported by lung biopsy findings.

CASE PRESENTATION

A woman in her late 40s was referred to our department with multiple abnormal findings on high-resolution CT (HRCT). She had undergone abemaciclib treatment for 10 months to prevent breast cancer recurrence following surgery and chemoradiation therapy and had no history of respiratory symptoms. She had also received a gonadotropin-releasing hormone agonist and fulvestrant, which is an estrogen receptor down-regulator, as part of a 13-month-long endocrine therapy.

She was an ex-smoker (8 pack-years), did clerical work, had no pets and received no other medications. Her percutaneous oxygen saturation was 98% and physical examination did not reveal any rales or other abnormal findings.

INVESTIGATIONS

Chest radiography revealed consolidation and reticular shadow in the lower left field (figure 1, arrowhead), while chest HRCT revealed bilateral multiple non-segmental GGOs and consolidation with an organising pneumonia (OP) pattern (figure 1, arrows). During the 10-month treatment, HRCT revealed recurrence of a partly appearing and disappearing GGO and consolidation (figure 2). Laboratory data showed no active inflammation (white cell count in 3.7×10^9/L and C reactive protein 0.1 mg/dL), but Krebs von den Lungen-6 (KL-6) and surfactant protein (SP)-D were positive (756 U/mL and 139.4 ng/mL, respectively); no infections were evident. Autoantibodies for collagen vascular diseases were also negative. From these findings, drug-induced pneumonitis due to abemaciclib was considered as the first differential diagnosis. We then discontinued abemaciclib and planned the bronchoscopic examination for 10 days later. Analysis of bronchoalveolar lavage (BAL) from the left S^8b bronchi revealed lymphocytosis (47%), but there was no evidence of infection or malignancy. A transbronchial lung biopsy from the left B^9a and B^8b bronchi revealed alveolitis along with epithelial cell injury. Several lymphocytes had infiltrated into the alveolar walls and surrounding peripheral vascular vessels; the alveolar epithelial cells were swollen and regenerated with cuboidal metaplasia (figure 3). These changes were distinguished clearly from the normal alveolar tissue. The drug-induced lymphocyte stimulation test for abemaciclib was negative.

DIFFERENTIAL DIAGNOSIS

For the differential diagnosis for multiple non-segmental GGOs and consolidation, drug-induced pneumonitis, radiation-induced pneumonitis, connective tissue disease-associated interstitial disease, hypersensitivity pneumonitis, eosinophilic pneumonia, infection, and sarcoidosis were considered.

The patient was treated for insomnia and seasonal allergic rhinitis with flunitrazepam and antihistamine for several years. Abemaciclib had been administered most recently. We could not identify any cause for hypersensitive pneumonitis based on her medical history and living environment.

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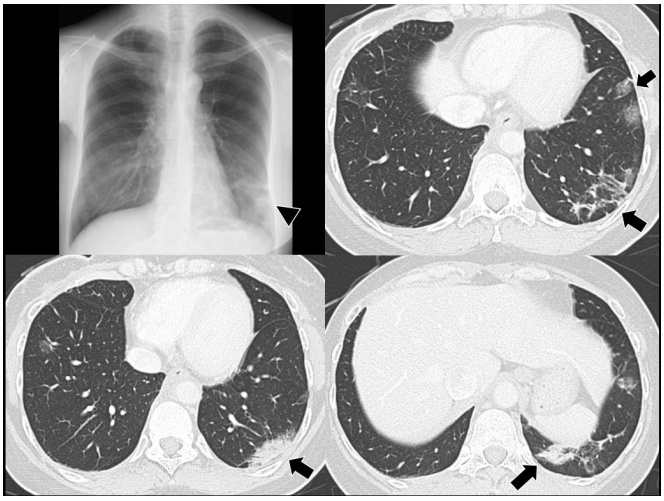

Figure 1 Chest radiography and high-resolution CT (HRCT) at the time of consultation. Chest radiography revealed consolidation and reticular shadow in the left lower field (arrowhead), while HRCT showed bilateral multiple non-segmental ground-glass opacities and consolidation (arrows).

Her laboratory data, analysis of BAL and histology from lung biopsy were unlikely for eosinophilic pneumonia or infection. Her physical findings and autoantibodies for collagen vascular diseases did not suggest complication of collagen vascular diseases. Her chest CT did not reveal mediastinal lymphadenopathy, and no granuloma was seen in lung biopsy. Although the drug-induced lymphocyte stimulation test was negative, it was performed during the treatment with prednisolone and under the effect of prednisolone on lymphocytes; therefore, the result could have been false negative.

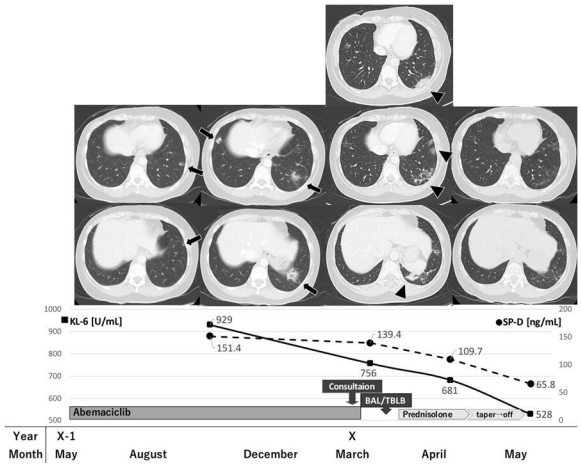

Figure 2 Clinical course with HRCT findings. At the time of consultation (March, year X), chest HRCT showed bilateral multiple non-segmental GGOs and consolidation (arrowheads). On comparison of the chest CT obtained at 3 months (August, year X-1) and 7 months (December, year X-1) post-abemaciclib initiation, multiple GGOs and consolidation were seen in a different area (arrows). After treatment with prednisolone for 1.5 months, GGO and consolidation had disappeared (May, year X). BAL, bronchoalveolar lavage; GGOs, ground-glass opacities; HRCT, high-resolution CT; KL-6, Krebs von den Lungen-6; SP, surfactant protein; TBLB, transbronchial lung biopsy.

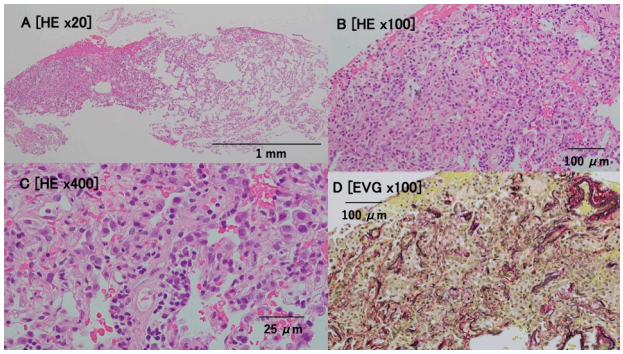

Figure 3 Histological findings from transbronchial lung biopsy from the left B^8b and B^9a bronchi. At low-power field (A), a lesion of pneumonitis was distinguished from the normal alveolar tissue. At high-power field (B,C), several lymphocytes had infiltrated into alveolar walls and surrounding peripheral vascular vessels. Alveolar epithelia changed into the cuboidal-shaped cells. Elastica van Gieson (EVG) stain (D) showed no fibrotic changes in interstitial tissue.

TREATMENT

Consequently, we diagnosed with a mild form of drug-induced pneumonitis due to abemaciclib administration, which was graded as grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events.[2 3] However, since HRCT yielded remarkable findings, we administered moderate-dose prednisolone (0.5 mg/kg/day).

OUTCOME AND FOLLOW-UP

The previously observed abnormal radiographic shadows rapidly disappeared; consequently, we tapered and discontinued prednisolone after 6 weeks. KL-6 and SP-D decreased to within the normal range. The aromatase inhibitor letrozole was used to further treat breast cancer. Chest HRCT revealed no pneumonitis recurrence post-steroid therapy (figure 2).

DISCUSSION

Abemaciclib has been approved for hormone receptor-positive human epidermal growth factor receptor 2-negative advanced or recurrent breast cancer. A post-marketing surveillance in Japan reported pulmonary toxicity (1.7%) and mortality (0.3%) after abemaciclib administration,[1] which led to the issuance of the Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter). The drug-induced pneumonitis onset in these cases began mostly within 5 months of treatment initiation, with concurrent dyspnoea, cough, fever and general fatigue. The chest HRCT findings showed the following patterns: diffuse alveolar damage (DAD), OP, a faint GGO and a non-specific interstitial pneumonia pattern. The DAD pattern was dominant in fatal cases. Steroid hormones were administered in 68% of cases, following which 56% of them improved; however, no improvements were observed in 12%, whereas 30% exhibited fatality. Age (>70 years), pre-existing interstitial disease and Eastern Cooperative Oncology Group Performance Status >2 were identified as risk factors for mortality.[1] Furthermore, abemaciclib is reportedly associated with a 4.7-fold greater risk of drug-induced pneumonitis than other cancer agents.[4] From the evaluation of the Japanese Adverse Drug Event Report database, treatment with abemaciclib is associated with drug-induced pneumonitis regardless of age.[5] For management of interstitial lung disease/pneumonitis as adverse events, HRCT, BAL and/or biopsy are indicated.[6] Our patient was considered a mild case of

pneumonitis without clinical symptoms. However, since extensive abnormal shadows appeared during abemaciclib administration, a steroid hormone was administered instead. To the best of our knowledge, this is the first case report of drug-induced pneumonitis due to abemaciclib administration with lung biopsy findings. In one report of drug-induced pneumonitis due to abemaciclib administration, biopsy was impossible due to the severity of pneumonitis.[7] Another case of drug-induced eosinophilic pneumonia due to abemaciclib administration was diagnosed by only BAL.[8] Upon comparing the HRCT and histological findings, it was concluded that HRCT alone could not predict the histological pattern.[9] HRCT in the present case exhibited an OP pattern, but histological analyses confirmed the presence of alveolitis along with epithelial cell injury, which suggested a good prognosis following steroid treatment. Although no interstitial changes were seen before treatment with abemaciclib, follow-up CT during treatment with abemaciclib revealed the recurrence of GGOs and consolidation without clinical symptoms. Had abemaciclib treatment been continued without steroid administration, the epithelial damage might have led to DAD, resulting in severe pneumonitis. In this case, follow-up CT during treatment and transbronchial lung biopsy were useful for the diagnosis and decision-making in the treatment of drug-induced pneumonitis due to abemaciclib administration.

KL-6 and SP-D levels were positive during treatment with abemaciclib prior to consultation with us and improved with treatment (figure 2). KL-6 is an MUC1 mucin protein and has been observed in adenocarcinoma of various cancer cell lines, including breast cancer,[10] whereas SP-D is considered a useful marker of drug-induced pneumonitis.[11] Since the severity of abemaciclib-induced pneumonitis ranges from mild to fatal, monitoring these multiple diagnostic arms and collaborative consultation with pulmonologists may be highly effective in preventing drug-induced pneumonitis.

In conclusion, when abemaciclib is administered, monitoring drug-induced pneumonitis with regular chest radiographs and HRCT imaging, along with KL-6 and SP-D assessment, is necessary for the prevention of extensive pneumonitis. Histological findings from lung biopsy are also useful for diagnosis and treatment.

Patient's perspective

I was totally asymptomatic and so surprised that I've got pneumonitis from abemaciclib administration. From the beginning of treatment with abemaciclib, the doctors and pharmacists told me to be aware of dyspnea, fever, and cough, which suggest abemaciclib-induced pneumonitis.

Monitoring HRCT and consultation to respiratory medicine could help me from advance to severe pneumonitis without notice.

I hope my experience and clinical course will help safe and effective treatment with abemaciclib in future.

Learning points

- Abemaciclib-induced pneumonitis can range from mild to fatal.
- When abemaciclib is administered, monitoring drug-induced pneumonitis with regular chest radiographs and high-resolution CT imaging, along with Krebs von den Lungen-6 and surfactant protein-D assessment, is necessary for the prevention of extensive pneumonitis.
- If possible, histology from lung biopsy also helps to improve treatment outcome of abemaciclib-induced pneumonitis.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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