Afatinib treatment of severe respiratory failure due to malignant lymphangitis in a dialysis patient with squamous cell carcinoma of the lung

Osamu Kanai, Mitsuteru Koizumi, Takanori Ito, Tadashi Mio

SUMMARY
Patients on dialysis have limited treatment options for advanced lung cancer because some chemotherapeutic agents are unavailable due to renal dysfunction. A man in his 70s on peritoneal dialysis presented with persistent fever refractory to antibiotics for 2 weeks. Subsequent whole-body CT showed a 5 cm diameter mass in the right lower lobe of the lung with right-sided pleural effusion and osteolytic metastasis of the right iliac bone. The patient was diagnosed with squamous cell carcinoma (cT3N2M1, stage IVB) harbouring the p.Gly719Ala point mutation on exon 18 of the epidermal growth factor receptor. The patient developed severe respiratory failure due to malignant lymphangitis after a bronchoscopy. He received 30 mg/day of afatinib, resulting in tumour shrinkage and recovery from respiratory failure. We advocate for aggressive screening of driver oncogenes in patients with lung cancer on dialysis, including those with squamous cell lung cancer.

BACKGROUND
Lung cancer is often diagnosed in its advanced stage, and chemotherapy remains the primary treatment modality. Advances in chemotherapy have led to the development of several treatment options, including molecular targeted agents and immune checkpoint inhibitors (ICIs), for non-small cell lung cancer (NSCLC). Precision medicine is now offered to select patients with NSCLC based on targeted oncogene profiles. However, patients with impaired visceral function, such as those on dialysis, have limited treatment options for advanced lung cancer.

Afatinib is a second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), one of the major molecular targeted agents in NSCLC. Afatinib is effective not only in NSCLC cases that harbour the EGFR major mutations, but also in those with minor mutations. Furthermore, afatinib can be safely administered to patients on dialysis. However, the diagnosis of complications related to lung cancer can be challenging in these patients as there are additional differential diagnoses that are specific to such patients.

CASE PRESENTATION
A man in his 70s with type 2 diabetes mellitus-induced renal failure and on peritoneal dialysis presented with a persistent fever refractory to treatment with intravenous ceftriaxone administration for 2 weeks at a previous hospital. Whole-body CT on admission to our hospital showed a 5 cm diameter mass in the right lower lobe of the lung with right-sided pleural effusion, while there were no findings suggestive of the cause of the fever, such as abscesses or thickening of the peritoneum in the abdomen (figure 1). We performed thoracic drainage of the right pleural effusion and switched the antibiotics to ampicillin and sulbactam. The pleural effusion sample indicated exudate, but the cytology showed no malignant cells and the culture showed no pathogenic bacteria (table 1). After the fever resolved and the pleural effusion decreased, the patient developed another fever 1 week after completing antibiotic therapy. On collecting the pleural effusion again, its appearance and concentration of electrolytes were equivalent to those of the peritoneal dialysis solution (table 1). Furthermore, the glucose concentration in the pleural fluid was approximately twice as high as that in the serum, leading us to diagnose diaphragmatic fistula as the cause of the pleural effusion. Peritoneal dialysis was continued because shunting had not been performed for the patient. We could not confirm the cause of the fever, although the patient was discharged after a week of antibiotic treatment which resolved the fever. To diagnose the mass and cause of the fever, we planned to perform a bronchoscopy.

INVESTIGATIONS
Two weeks after discharge, the patient presented with general malaise and fever. Subsequently, a serum sample test indicated a decreased serum albumin level of 1.3 g/dL (lower limit of normal: 4.0 g/dL), indicating peritoneal dysfunction for dialysis. The patient was admitted to our hospital again and was initiated blood dialysis through a cervical vascular access catheter. To further investigate the cause of his symptoms, we performed a bronchoscopy, which revealed a mass occlusion of the right lower lobe (figure 2). The tissue sample obtained by the bronchoscopy confirmed the diagnosis of squamous cell carcinoma of the lung, while no bacteria were detected in the bronchial lavage fluid cultures (figure 3A). Immunohistochemical analysis of the programmed cell death

© BMJ Publishing Group Limited 2024. No commercial re-use. See rights and permissions. Published by BMJ.


Kanai O et al. BMJ Case Rep 2024;17:e253308. doi:10.1136/bcr-2022-253308
ligand-1 (22C3) indicated a 100% tumour proportion score (figure 3B). Additionally, the tissue sample was positive for the G719A point mutation in exon 18 of the EGFR. A whole-body CT performed on admission showed osteolytic metastasis of the right iliac bone, confirming the diagnosis of stage IVB (cT3N2M1b based on the eighth edition of the Union for International Cancer Control’s tumour, node, metastases staging system) (figure 4). Naproxen, administered after diagnosing the cause of the fever as paraneoplastic, immediately resolved the fever. However, while awaiting tumour genetic testing, the patient developed severe respiratory failure and required oxygenation with a reservoir mask at 12 L/min. Chest radiography revealed diffuse ground glass opacity in the bilateral lungs without increased right pleural effusion. We performed ECG and echocardiography to differentiate pulmonary oedema associated with congestive heart failure. The ECG showed normal sinus rhythm, and the echocardiography displayed a left ventricular ejection fraction of 67%. Moreover, even though we reduced the dry weight by 0.5 kg for each dialysis session after the patient developed severe respiratory failure, the ground glass opacity remained unchanged. A series of examinations and treatment course suggested that the ground glass opacity was caused by malignant lymphangitis (figure 5A).

**TREATMENT**

Given the positivity in EGFR mutation, we initiated treatment with 30 mg/day of afatinib. In Japan, the insurance indication for afatinib is ‘inoperable or recurrent NSCLC with EGFR mutation-positive’. Since the patient was diagnosed with NSCLC harbouring EGFR G719A, the use of afatinib was within the insurance indication, not an off-label use of the drug.

**OUTCOME AND FOLLOW-UP**

On initiating afatinib treatment, the patient’s oxygen demand gradually improved, along with a decrease in the ground glass opacity in the bilateral lungs (figure 5B). The patient achieved tumour shrinkage and recovered from respiratory failure after 1 month. He was discharged from our hospital 2 weeks after undergoing surgical shunting. He continued the afatinib treatment without severe adverse events for over 3 months.

**DISCUSSION**

We report a case of a patient diagnosed with lung squamous cell carcinoma harbouring EGFR G719A who received successful treatment with afatinib. The patient presented with fever and pleural effusion during treatment, which posed diagnostic challenges. Moreover, managing the patient with peritoneal dysfunction and severe respiratory failure due to malignant lymphangitis required careful consideration. Despite the patient’s poor performance status (PS) due to severe respiratory failure, afatinib demonstrated rapid and remarkable efficacy with minimal adverse events. Generally, molecular targeted

![Figure 1](image1.jpg) A CT image of the lower lobes of the lung. Whole-body CT taken on the initial admission revealed a 5 cm diameter mass in the lower lobe of the lung with right pleural effusion.

![Figure 2](image2.jpg) Images of the right lower bronchus taken during bronchoscopy. The images display a mass occlusion of the right lower lobe (B9), suggesting lung cancer.

**Table 1. Composition of serum, pleural fluid and peritoneal dialysis solution**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Serum</th>
<th>Pleural fluid</th>
<th>Peritoneal dialysis solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dL)</td>
<td>5.4</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>1.4</td>
<td>0.8</td>
<td>–</td>
</tr>
<tr>
<td>Lactate dehydrogenase (IU/L)</td>
<td>220</td>
<td>142</td>
<td>–</td>
</tr>
<tr>
<td>Sodium ion (mEq/L)</td>
<td>130</td>
<td>131</td>
<td>132</td>
</tr>
<tr>
<td>Potassium ion (mEq/L)</td>
<td>3.1</td>
<td>3.5</td>
<td>0</td>
</tr>
<tr>
<td>Chloride ion (mEq/L)</td>
<td>92</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>128</td>
<td>234</td>
<td>1500</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (ng/ mL)</td>
<td>4.0</td>
<td>3.6</td>
<td>–</td>
</tr>
<tr>
<td>Squamous cell carcinoma antigen (ng/mL)</td>
<td>2.0</td>
<td>3.7</td>
<td>–</td>
</tr>
<tr>
<td>Neutrophil fraction (%)</td>
<td>–</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>Lymphocyte fraction (%)</td>
<td>–</td>
<td>71</td>
<td>–</td>
</tr>
<tr>
<td>Culture</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Cytology</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
</tbody>
</table>

therapy offers faster and more efficacious treatment option than cytotoxic chemotherapy, especially for patients with poor PS.10

Despite the squamous cell carcinoma, the patient harboured EGFR G719A. The efficacy of afatinib in NSCLC harbouring EGFR G719A has been described.3–5 The prevalence of EGFR mutations in adenocarcinoma is approximately 50%, whereas the prevalence in squamous cell carcinoma is approximately 4%.11 Although EGFR mutations in squamous cell carcinoma are rare, recent guidelines recommend testing for driver oncogenes in these patients.1,12 In fact, the prognosis of lung squamous cell carcinoma harbouring EGFR mutations is generally poor; however, treatment with EGFR-TKIs in these patients may lead to better outcomes than without EGFR-TKI use.13 Therefore, we should aggressively explore driver oncogenes, especially in patients with limited treatment options such as those with poor PS or on dialysis.

In the present case, the patient’s peritoneal dysfunction necessitated switching to haemodialysis during hospitalisation. Despite the limited treatment options for patients with severe renal failure, EGFR-TKIs and ICIs are available for these patients.7 We chose afatinib not only due to its rapid and drastic efficacy, but also to avoid the disadvantages of ICIs. First, the efficacy of ICIs is reported to be inferior in those with poor PS.14–16 Second, the

Figure 3 Images of the tissue sample obtained by bronchoscopy. The tissue sample was obtained by a transbronchial biopsy taken in the lower lobe of the lungs. H&E staining of the tissue showed atypical cells, suggesting squamous cell carcinoma (A). The tissue immunohistochemical stain for programmed cell death ligand-1 (PD-L1; 22C3) indicated a tumour proportion score of 100% (B).

Figure 4 A CT image of the pelvic region. Whole-body CT taken on the second admission showed an osteolytic metastasis of the right iliac bone.

Figure 5 Chest radiography images taken before and after the initiation of afatinib therapy. Chest radiography performed after severe respiratory failure displayed diffuse ground glass opacity in the bilateral lungs without increased right pleural effusion (A). The findings did not change after haemodialysis, suggesting malignant lymphangitis. One month after initiating treatment with afatinib, the ground glass opacity in the bilateral lungs improved (B).
therapeutic effect of ICI may be delayed and temporarily hyperprogressive. The treatment course of ICI may cause drug-induced interstitial lung diseases, as observed in the combination of durvalumab and osimertinib.

Diagnosing the patient was challenging due to the variety of diagnoses. We initially considered lung abscess and pyothorax, lung cancer, malignant pleuritis and paraneoplastic fever. However, we had to add a diaphragmatic fistula to the differential diagnoses because the patient was on peritoneal dialysis.

Eventually, the patient was diagnosed with lung cancer and paraneoplastic fever, as the fever did not respond to repeated antibiotic treatment and quickly resolved with administration of naproxen. Similarly, we clinically diagnosed malignant lymphangitis based on the rapid improvement of severe respiratory failure after the initiation of afatinib.

In conclusion, we should aggressively assess for driver oncogenes in patients with lung cancer on dialysis, even in cases of squamous cell carcinoma. Especially in cases of decreased PS, the chance of immediate effects after treatment with TKIs rather than ICI should be explored. Patients with lung cancer on dialysis require careful management due to the varied differential diagnoses of pleural effusions and ground glass opacity in the lungs.

Learning points

► Afatinib exerts efficacy against non-small cell lung cancer harbouring minor epidermal growth factor receptor (EGFR) mutations, including the G719A point mutation in exon 18, and can be administered to patients with lung cancer on dialysis.

► EGFR-tyrosine kinase inhibitors (TKIs) offer rapid and drastic efficacy with fewer incidences of adverse events than cytotoxic chemotherapy, even in patients with poor performance status.

► We should aggressively assess for driver oncogenes in patients with lung cancer on dialysis, even in cases of squamous cell carcinoma.

► The prognosis of lung squamous cell carcinoma harbouring EGFR mutations is generally poor, but treatment with EGFR-TKI may lead to better outcomes than without EGFR-TKI use.

► Patients with lung cancer on dialysis require careful management due to the varied differential diagnoses of pleural effusions and ground glass opacity in the lungs.

Contributors OK was responsible for drafting the text, sourcing and editing the clinical images, investigating the results, drawing the original diagrams and algorithms, and critically revising for important intellectual content. OK, MK, TI and TM gave final approval of the manuscript.

Funding This report was partially supported by the National Hospital Organization’s fiduciary funds for English proofreading.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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.

ORCID iD Osamu Kanai http://orcid.org/0000-0003-0736-3317

REFERENCES


