# Acute lung injury as an adverse event of gefitinib

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**Gefitinib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, is an effective treatment for patients with non-small cell lung cancer (NSCLC). Some investigators have recently reported several patients complicated by acute lung injury after the initiation of gefitinib administration. In this report, we investigated the efficacy and adverse events during treatment with gefitinib. The subjects of this study were all of the 110 patients with NSCLC who were treated in our hospital and its eight branch hospitals. Patients received gefitinib at a dose of 250 mg once daily. The response rate was 30%. The frequently reported adverse events were skin disorders, gastrointestinal disturbances, liver dysfunction and acute lung injury. Five of the 12 patients who were considered to have suffered acute lung injury died of progressive respiratory failure. Of the nine patients who had pulmonary fibrosis before use of gefitinib, five developed acute lung injury during the treatment. Sera from three of the 12 patients were evaluated and all three showed increases of surfactant protein (SP)-A, SP-D and KL-6. We conclude that gefitinib was clinically useful. However, several patients suffered acute lung injury which could have been caused by gefitinib. A detection system including SP-A, SP-D and KL-6 as prime candidates as markers should be established as promptly as possible. Clinicians should be aware that treatment of NSCLC with gefitinib involves the risk of acute lung injury and therefore careful consideration should be given before deciding whether or not gefitinib is indicated for treatment. Further study is necessary to elucidate the mechanism of acute lung injury by gefitinib.**


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## Introduction

Gefitinib, an orally selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TKI), is an effective treatment for patients with advanced non-small cell lung cancer (NSCLC). In Japan, gefitinib was approved for patients with NSCLC on 5 July 2002 following the completion of successful clinical trials and it is now being used as the second line of chemotherapy for this disease. Gefitinib has been regarded as a safe agent with mild adverse events such as skin disorders, gastrointestinal disturbances and liver dysfunction [1–3]. Recent investigations, however, revealed that gefitinib induced acute lung injury and acute interstitial pneumonia, which often resulted in death [4,5]. In order to re-evaluate the efficacy and adverse events of this agent, we investigated the effects of its administration on patients with NSCLC.

## Patients and methods

### Patients

All of the 110 patients with locally advanced and/or metastatic NSCLC who were treated in our hospital and its eight branch hospitals between September 2002 and December 2002 were investigated. Patients had either a histologically or cytologically confirmed diagnosis of stage IB, IIIA, IIIB or IV NSCLC that was not curable with surgery or a recurrence of NSCLC. Table 1 shows patient characteristics. Nine patients were complicated with pulmonary fibrosis and none of them had been treated with steroid or other therapies before use of gefitinib. Sixty-nine patients underwent systemic anticancer chemotherapy and/or radiotherapy prior to use of gefitinib. The minimal interval between the end of prior therapy and the start of treatment with gefitinib was 28 days. All patients gave informed consent to the use of gefitinib.

Presently, use of gefitinib is recommended generally as a second or third line. However, in Japan, gefitinib had been regarded as a safe agent until a review of severe lung injury was reported by the Pharmaceuticals and Medical Devices Evaluation Center [6]. All patients enrolled in our study received it up to December 2002 before release of the report. Therefore, some patients with poor performance status (PS) received oral administration of

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**Table 1 Patient characteristics**

| | *n* | % |
|---|---|---|
| Age (years) | | |
| median | 67 | |
| range | 37–83 | |
| Sex | | |
| male | 69 | 62.7 |
| female | 41 | 37.3 |
| WHO performance status | | |
| 0 | 37 | 33.6 |
| 1 | 37 | 33.6 |
| 2 | 21 | 19.2 |
| 3 | 12 | 10.9 |
| 4 | 3 | 2.7 |
| Histological type | | |
| adenocarcinoma | 81 | 73.6 |
| squamous cell carcinoma | 24 | 21.8 |
| large cell carcinoma | 4 | 3.6 |
| poorly differentiated carcinoma | 1 | 0.9 |
| Stage | | |
| IB | 2 | 3.6 |
| IIIA | 17 | 15.5 |
| IIIB | 19 | 16.4 |
| IV | 72 | 64.5 |
| Prior treatment | | |
| chemotherapy | 43 | 39.1 |
| chemotherapy and radiotherapy | 19 | 17.3 |
| surgery | 8 | 7.3 |
| surgery and chemotherapy | 5 | 4.5 |
| surgery and chemotherapy and radiotherapy | 2 | 1.8 |
| no treatment | 33 | 30.0 |

gefitinib preferably rather than systemic chemotherapies as first line. As a result, patients who received it as first line were unexpectedly lost (30% of the enrolled patients in this study).

### Treatment

Gefitinib was administered orally at a dose of 250 mg once daily. Treatment was continued until disease progression, the appearance of unacceptable toxicity or patient's withdrawal of consent. During the treatment period no other medication with known or presumed activity against NSCLC was allowed.

### Assessment

Baseline assessment was necessary for all patients and comprised the following: medical history, including prior anticancer therapy and radiotherapy, physical examination and vital signs, PS, blood cell count and blood biochemistry, urinalysis, chest X-ray and/or computed tomography (CT) scan, abdominal CT scan, brain magnetic resonance imaging, electrocardiogram, and pulmonary function test. These assessments were repeated appropriately during the treatment.

### Toxicity and efficacy

All adverse events were recorded according to the National Cancer Institute common toxicity criteria (NCI-CTC version 2.0). WHO evaluation criteria were used for efficacy analysis [7].

### Statistical analysis

Descriptive statistics for the patient group are reported as mean, median and range. Statistical comparisons between group rates (proportions) were assessed by Person's $\chi^2$ test or Fisher's test where appropriate.

## Results

None of the patients achieved a complete response. Thirty-three patients (30.0%) achieved a partial response (PR) and 39 patients (35.5%) had stable disease (SD) as their best response. Thirty-eight patients (34.5%) had progressive disease (PD) (Table 2). There was a statistically significant difference in response rate (RR) between female gender (22 of 41 patients: 53.6%) versus male gender (14 of 69 patients: 20.3%) ($p = 0.006$). RR was not statistically associated with any of the following prognostic factors: histology (adenocarcinoma versus others) ($p = 0.24$), disease stage (IB and IIIA versus IIIB and IV) ($p = 0.52$) or PS (0–1 versus 2–4) ($p = 0.37$). The patients with adenocarcinoma showed a higher RR (27 of 81 patients: 33.3%) than those with squamous cell carcinoma (four of 24 patients: 16.6%), but the difference was not statistically significant ($p = 0.13$).

With the exception of acute lung injury, the adverse effects of gefitinib were mild (grade 1/2) and reversible on cessation of treatment. They consisted of skin disorders including acne-like rash, pruritus and dry skin in 67 patients (60.9%), gastrointestinal disturbances including diarrhea, nausea, vomiting and anorexia in 22 patients (20.0%), liver dysfunction (increased hepatic enzymes) in 15 patients (13.6%), and acute lung injury in 12 patients (10.9%).

Table 3 shows the characteristics of the 12 patients who developed acute lung injury during treatment with gefitinib. These patients developed rapidly progressive dyspnea with severe hypoxemia and diffuse new ground-glass attenuation (GGA) on chest CT findings (Fig. 1).

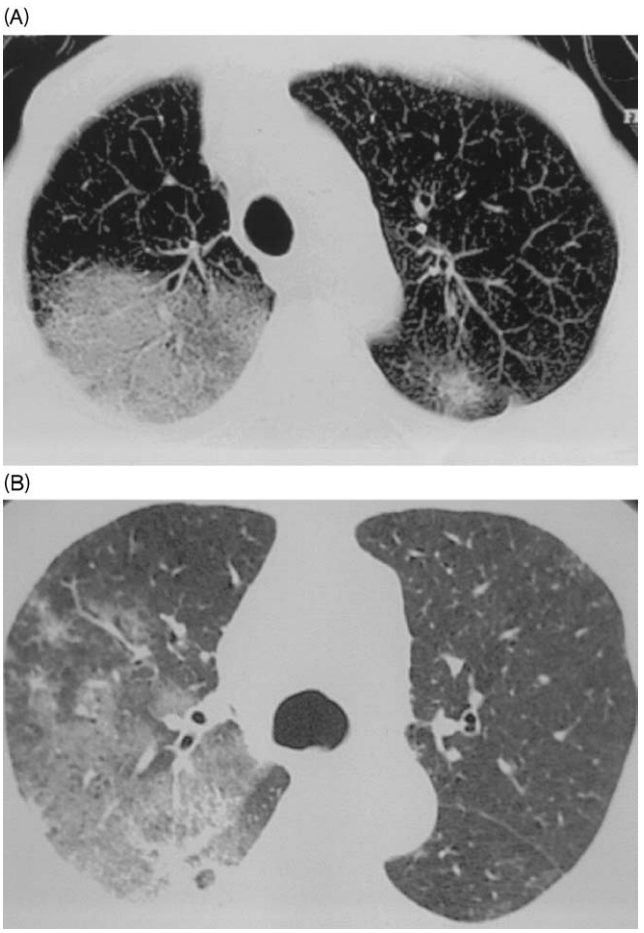
**Table 2 Efficacy of gefitinib**

| | *n* | % |
|---|---|---|
| Adenocarcinoma | 81 | |
| PR | 27 | 33.3 |
| SD | 28 | 34.5 |
| PD | 26 | 32.2 |
| Squamous cell carcinoma | 24 | |
| PR | 4 | 16.6 |
| SD | 9 | 37.5 |
| PD | 11 | 45.9 |
| Large cell carcinoma | 4 | |
| PR | 2 | 50.0 |
| SD | 1 | 25.0 |
| PD | 1 | 25.0 |
| Poor differential carcinoma | 1 | |
| SD | 1 | 100 |
| Total | 110 | |
| PR | 33 | 30.0 |
| SD | 39 | 35.5 |
| PD | 38 | 34.5 |

The period of administration before the development of acute lung injury varied significantly among the cases, with the shortest and longest periods being for several days and for more than 3 months, respectively. The complication of respiratory tract infections and rapid progression of lung cancer including lymphangitis carcinomatosa had not been demonstrated on findings of serial chest radiographs, general blood tests, tumor markers, and sputum culture of bacteria and fungi. Nine of the 110 patients had pulmonary fibrosis prior to use of gefitinib and five of these nine developed acute lung injury during the treatment. There was a statistically significant difference in the incidence rate of acute lung injury between the patients with pulmonary fibrosis (five of nine patients; 55.6%) and those without it (seven of 101 patients; 6.9%) ($p = 0.006$). One patient (patient 6) was irradiated 4 months before use of gefitinib, and the radiated parts were the primary tumor lesion and mediastinal lymph node metastasis. At the completion of irradiation, radiation fibrosis occurred, but it was not a PD. Chemotherapeutic agents had been used in five patients (patients 3, 4, 6, 8 and 10) more than 6 weeks prior to the administration of gefitinib. The histories of these patients and the clinical examinations conducted did not provide any evidence of adverse effects of medication prior to treatment with gefitinib. The acute lung injury was, thus, likely essentially caused by the treatment with gefitinib. Of the 12 patients who had lung injury, seven never received any previous therapy, because of poor PS and/or debilitating pre-existing conditions like pulmonary fibrosis. The lung injury occurred more frequently in patients with PS 2–4 (seven of 36 patients: 19.4%) than in those with PS 0–1 (five of 74 patients: 6.8%) although the difference was not statistically significant ($p = 0.056$). Frequency of acute lung injury in male gender (10 of 69 patients: 14.5%) was higher than in female gender (two of 41 patients: 4.8%), but the difference was not statistically significant ($p = 0.21$).

The specific serum markers of pulmonary fibrosis, termed surfactant protein (SP)-A, SP-D and KL-6 were measured in three of the 12 patients (patients 1, 2 and 10). At the time of initiation of gefitinib administration all of these three patients exhibited high concentrations of at least

**Fig. 1**




Chest CT scans of the patients who have developed acute lung injury during treatment with gefitinib (A and B show patients 1and 7, respectively). Pulmonary infiltrates on the chest radiograph were apparent after administration of gefitinib. Chest CT scans showing diffuse GGA in the lung fields.

**Table 3 The characteristics of the 12 patients who have developed acute lung injury during treatment with gefitinib**

| Patient | Age (years) | Sex | Histology (cancer) | Efficacy of gefitinib | Period (days)[a] | Pulmonory comorbidities | Prior therapy | Course of lung injury |
|---|---|---|---|---|---|---|---|---|
| 1 | 76 | M | squamous | NC | 12 | PF | none | dead |
| 2 | 76 | M | adeno | NC | 14 | PF | none | dead |
| 3 | 76 | M | adeno | NC | 12 | PF | chemotherapy | improved |
| 4 | 69 | M | large | NC | 50 | | chemotherapy | improved |
| 5 | 66 | M | adeno | PD | 124 | PF | none | improved |
| 6 | 68 | M | adeno | NC | 12 | RF[b] | CHT/TI | dead |
| 7 | 85 | M | adeno | NC | 36 | | none | dead |
| 8 | 74 | F | squamous | PR | 43 | | chemotherapy | improved |
| 9 | 72 | M | adeno | PD | 130 | | none | improved |
| 10 | 62 | M | squamous | NC | 73 | PF | chemotherapy | dead |
| 11 | 78 | F | adeno | PR | 43 | | none | improved |
| 12 | 82 | M | adeno | NC | 30 | | none | improved |

[a]The period of administration before the development of acute lung injury.
[b]RF means radiation fibrosis. At the completion of irradiation, radiation fibrosis occurred, but it was not PD. PR: partial response, NC: no change; PD: progressive disease; PF: pulmonary fibrosis; CHI: chemotherapy; TI: thoracic irradiation, squamous: squamous cell carcinoma; Adeno: adenocarcinoma; large: large cell carcinoma.

one of the markers, as shown in Figure 2. After the occurrence of acute lung injury, all the patients exhibited increases in the concentrations of the markers, with the exception of SP-A in patient 2. All of these patients finally died of progressive respiratory failure.

Of the 12 patients who had acute lung injury, five died of progressive respiratory failure. High-dose steroids given were not effective. Among the patients that died, the average period between confirmation of acute lung injury and death was 10.6 days (median 7 days: range 6–23) and lung injury progressed rapidly in many patients. Postmortem autopsy was conducted on only one patient (patient 7) and histopathology of lung tissue showed diffuse alveolar damage (DAD). DAD with hyaline membranes, edema and thickening of the alveolar walls was observed in the area giving rise to the GGA on chest CT scan (Fig. 3). The histopathologic analysis of lung tissue did not reveal any lymphangitic spread of the cancer or infectious etiology.

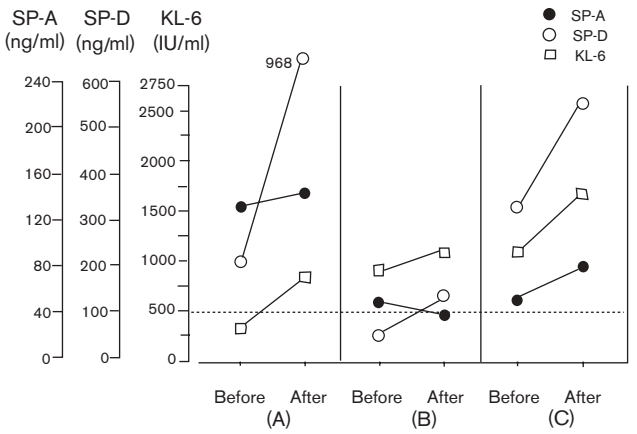
## Discussion

Gefitinib is an orally selective inhibitor of EGFR-TKI. EGFR is expressed in a wide range of solid tumors including 40–80% of NSCLC [8–10]. Enhanced EGFR drive seems to promote tumor growth by increasing cell proliferation, motility [11], adhesion and invasive capacity [12], and by blocking apoptosis [13]. Gefitinib blocks signal transduction pathways implicated in promoting cancer growth, leading to decreased cellular proliferation, angiogenesis, tumor invasion and metastasis, and increased apoptosis [14,15].

Several phase I studies demonstrated that gefitinib is well tolerated and provides clinically significant antitumor activity in patients with advanced NSCLC [16–20]. Results of two randomized double-blind phase II trials, named IDEAL 1 and IDEAL 2, showed that gefitinib was effective for patients with advanced NSCLC who did not respond to platinum-based chemotherapy and that its toxicity was mild [1–3]. On the basis of these data, gefitinib was first approved in Japan for treatment of NSCLC on 5 July 2002. In IDEAL 1, in which 250 mg/day gefitinib was used as the second or third line of chemotherapy, 18.4% of patients achieved a PR [1,2]. In IDEAL 2, used as the third or fourth line of chemotherapy, 11.8% of the patients achieved a PR [3]. Previous studies [21,22] have identified two good prognostic factors for the use of gefitinib. One was female gender [21,22] and the other was pathohistological classification of adenocarcinoma [22]. In our investigation, 33 patients (30.0%) achieved a PR, suggesting that gefitinib has a significant antitumor activity and is clinically useful for the treatment of NSCLC. This agent appears to be particularly effective for the female gender with adenocarcinoma, as described in previous studies [21,22].

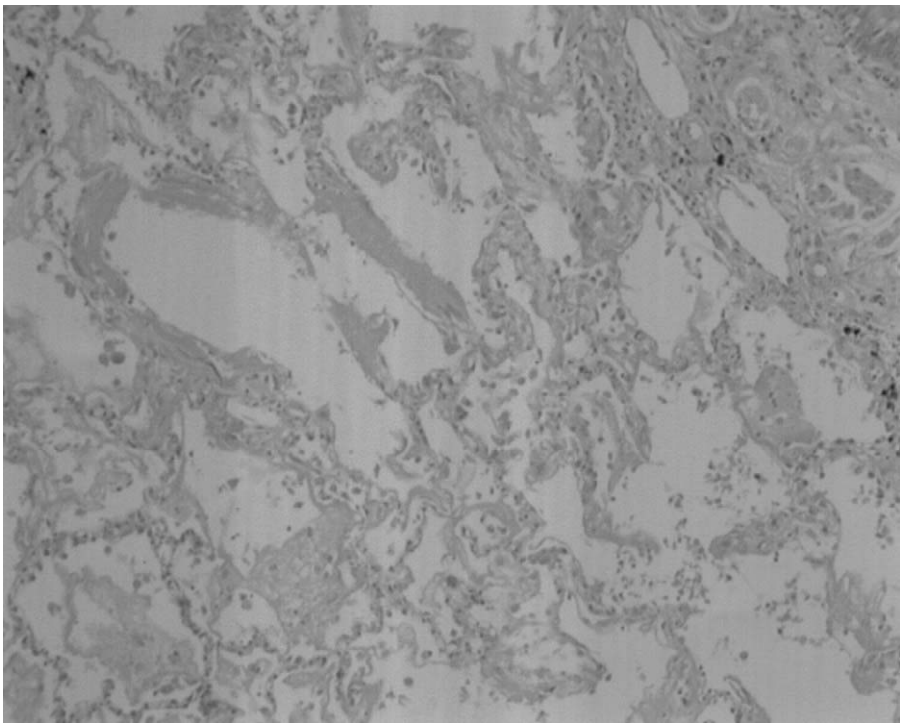
Adverse events of the skin, gastrointestinal tract and liver were observed frequently, but they were mild in severity and reversible. The characteristics of these adverse events were similar to those described in the previous studies [1–3,17,23,24]. The most serious complication of use of gefitinib, however, was acute lung injury, which was characterized by rapidly progressive dyspnea with severe hypoxemia and bilaterally extended GGA on radiography. Of the 110 patients with NSCLC who were treated in the 3 months between September and December 2002, 12 patients developed this disorder and five of these 12 have died as a result. The highest risk factor was the complication of chronic pulmonary fibrosis, which appeared to remain stable. Preceding chemotherapy and thoracic radiotherapy were not considered to affect the onset of acute lung injury, since the intervals between the end of preceded therapy and the start of gefitinib administration were long enough. Some previous studies [1,20,24] have also reported the complication of acute lung injury after the administration of gefitinib, but the authors did not think a causal relation with gefitinib existed. Recently, the Pharmaceuticals and Medical Devices Safety Information by the Japanese Ministry of Health, Labor and Welfare made public the occurrence of 291 cases of acute lung injury presumed to be associated with gefitinib [6]. At present the issue of lung involvement may be the largest concern regarding the use of this agent.

**Fig. 2**




SP-A, SP-D and KL-6 were measured in three cases of the patients with pulmonary fibrosis before treatment with gefitinib and after occurrence of acute lung injury (A, B and C show patients 1, 2 and 10, respectively). At the time of initiation of gefitinib administration, all of the three patients exhibited high concentrations of at least two of them, which were caused by the preceding pulmonary fibrosis. After the occurrence of acute lung injury, all patients exhibited increases of the concentrations excepted for SP-A in patient 2. Solid and open circles indicate SP-A and SP-D, respectively, and open squares indicate KL-6.

**Fig. 3**



Post-mortem histopathology of the lung tissue from patient 7 (hematoxylin & eosin stained × 100). A pattern of DAD, with hyaline membranes, epithelial desquamation, edema and thickening of the alveolar walls was observed.

The mechanism of the onset of acute lung injury associated with gefitinib remains to be clarified, but some mechanisms are hypothetically considered. EGFR existing through the cell membrane transmits an EGF signal forward downstream and activates cell growth. EGF is a potential factor promoting the regeneration of alveolar epithelial cells, which play a crucial role in the repair of acutely injured lungs [25,26]. It is known that EGFR is up-regulated in response to lung injury [27,28]. Thus, the EGFR inhibitor, gefitinib, may impair healing of epithelium and thereby exacerbate any existing lung injury, since it may act on alveolar epithelial cells as well as cancer cells. Basic studies using epithelial cell lines and animals *in vivo* are needed to verify this hypothesis.

The post-mortem autopsy conducted on one of patients who died of acute lung injury revealed histopathological findings of DAD and the same findings were obtained from previous gefitinib studies [4,5]. DAD is known to be the most severe histopathologic characteristic of acute lung injury and patients are poor responders in intensive care. DAD is also an essential histopathologic characteristic of acute exacerbation of idiopathic pulmonary fibrosis (IPF). Acute exacerbation is a major cause of death in patients with IPF and it is often triggered by complicated respiratory infection. Our investigation suggested that gefitinib is also a potential trigger of the acute exacerbation in patients with pulmonary fibrosis and that chronic interstitial inflammatory change primes the advance of DAD. This suggestion is supported by a report stating that apoptosis of type II pneumocytes could be the precipitating factor in the pathogenesis of IPF [29,30].

ELISAs for SP-A, SP-D and KL-6 were developed [31–33], and their clinical values have been evaluated for serological examinations for interstitial lung diseases [34–36]. The present study showed that SP-A, SP-D and KL-6 were increased in sera from patients with acute lung injury which occurred during gefitinib treatment. Although the number of patients in the present study was small, these findings suggest that the assay of these markers is helpful for detection of acute lung injury associated with gefitinib administration. More evidence based on serial measurements using many more cases is needed to clarify the clinical values and the difference in concentrations of these markers.

The overall incidence of acute lung injury in our study was 10.9%, which was higher than those in other previous studies [1,20,24]. For this reason, we speculate that the high incidence was caused mainly by entry of many patients with pre-existing pulmonary fibrosis and/or poor PS, which were risk factors of lung injury during

treatment with gefitinib. The other cause seems to be a difference in genetic factors. Even when nine patients with pulmonary fibrosis were excluded as subjects, the incidence was still high (6.9%: seven of 101). The importance of genetic factors on adverse reactions has been described in the use of anticancer drugs. For example, the adverse effect caused by CPT-11 is known to be dependent on polymorphism [37–40]. Future study should clarify the association with genetic factors showing a high risk of acute lung injury.

In conclusion, a molecule targeting anticancer agent, gefitinib, was demonstrated to provide therapeutic efficacy for NSCLC. However, acute lung injury as its adverse event was severe and occurred frequently in patients with pulmonary fibrosis. Clinicians should be aware of the risk of acute lung injury associated with treatment by gefitinib and should give careful consideration as to whether or not gefitinib is indicated, particularly in patients with pulmonary fibrosis. A system for detecting acute lung injury should be also established as promptly as possible, and SP-A, SP-D and KL-6 may be prime candidates. To improve the safety of use of this agent, investigators should attempt to identify in detail the clinical background and genetic factors which might predispose to acute lung injury by gefitinib. Moreover, markers with superior prognostic value for this disease should be established and the best method of prevention should be investigated urgently.

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