

1 **Successful erlotinib rechallenge for leptomeningeal metastases of lung**
2 **adenocarcinoma after erlotinib-induced interstitial lung disease. A case report and**
3 **review of the literature**

4

5 **Authors:**

6 Yosuke Togashi *, Katsuhiko Masago, Yasuhiro Hamatani, Yuichi Sakamori, Hiroki

7 Nagai, Young Hak Kim, Michiaki Mishima

8 Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University,

9 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan

10

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12

13 *** Corresponding author:**

14 Yosuke Togashi, M.D.

15 Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University,

16 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan.

17 Tel: +81-75-751-3830; Fax: +81-75-751-4643

18 E-mail: ytogashi@kuhp.kyoto-u.ac.jp

19

20 **Abstract**

21 The most serious adverse reaction associated with treatment with epidermal growth
22 factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is drug-induced interstitial lung
23 disease (ILD). Because EGFR-TKIs are key drugs for patients with non-small cell lung
24 cancer who have somatic activating mutations of the epidermal growth factor receptor
25 gene (*EGFR* mutations), several cases of retreatment with EGFR-TKIs after ILD
26 induced by these drugs have been reported. Here, we present a 68-year-old man with
27 lung adenocarcinoma and leptomeningeal metastases having an *EGFR* mutation who
28 was retreated with erlotinib after erlotinib-induced ILD. He suffered no ILD recurrence
29 and his leptomeningeal metastases dramatically improved. In addition to the present
30 case, reports of nine patients who were retreated with EGFR-TKIs after ILD were
31 found in the literature. Only one patient had recurrence of ILD (although seven were
32 retreated at a reduced dose of EGFR-TKIs, including the patient with recurrence). In
33 contrast, three patients had no recurrence of ILD even without dose-reduction. These
34 reports suggest that dose-reduction plays a limited role in preventing recurrence. Many
35 patients received corticosteroids during retreatment, but not the one with recurrence of
36 ILD. This may suggest that corticosteroids can prevent recurrence due to their

37 antiinflammatory properties.

38

39 *Key words:* epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib,

40 erlotinib, interstitial lung disease, rechallenge, epidermal growth factor receptor gene

41 mutation, leptomeningeal metastases

42

43 1. Introduction

44

45 Because patients with non-small cell lung cancer (NSCLC) who have somatic
46 activating mutations of the epidermal growth factor receptor (EGFR) gene (*EGFR*
47 mutations) generally respond to EGFR-tyrosine kinase inhibitors (EGFR-TKIs;
48 gefitinib or erlotinib) and can achieve long-term progression-free survival, the presence
49 of *EGFR* mutations is a very useful marker for facilitating the choice of treatment for
50 NSCLC [1-7]. Although systemic chemotherapy for leptomeningeal metastasis (LM)
51 has been thought to play a limited role because of the belief that the brain is a
52 pharmacologic sanctuary site, several studies have documented the effectiveness of
53 EGFR-TKIs in the treatment of LM of NSCLC with *EGFR* mutations [8-10].

54 The most common adverse events associated with treatment with EGFR-TKIs are
55 rash and diarrhea [11, 12]. Although not too frequent, the most serious adverse reaction
56 is drug-induced interstitial lung disease (ILD) [13-16]. Because EGFR-TKIs are key
57 drugs for patients with NSCLC having *EGFR* mutations, several cases of drug
58 rechallenge after ILD induced by EGFR-TKIs have been reported. Here, we present a
59 case report of a 68-year-old man with lung adenocarcinoma and LM having an *EGFR*

60 mutation who received erlotinib retreatment after erlotinib-induced ILD. No evidence
61 of ILD recurrence was seen, and his LM dramatically improved. We also review the
62 relevant published literature in this topic.

63

64 2. Case presentation

65

66 A 68-year-old Japanese man with a 40 pack-year history of smoking was diagnosed
67 with stage IV lung adenocarcinoma (bone metastases). After one cycle of ~~carboplatin-~~
68 ~~plus pemetrexed as~~ first-line cytotoxic chemotherapy, he suffered fatigue and
69 electrolyte abnormality (both grade 3) as complications and elected to discontinue
70 ~~these drugs~~ chemotherapy. *EGFR* mutational analysis revealed an exon 20 point
71 mutation (L858R), and he therefore started erlotinib at 150 mg daily. Although he
72 achieved a partial response (Fig 1A and 1B), he had cough and dyspnea on effort 8
73 weeks after initiation of erlotinib therapy. Chest computed tomography (CT) showed
74 bilateral air space consolidations (Fig. 1C). Bronchoalveolar lavage (BAL) fluid
75 contained no malignant cells and no pulmonary pathogens including bacteria, fungi,
76 and *Pneumocystis* were identified. The fraction of lymphocytes in BAL fluid was

77 increased to 60%. Therefore, erlotinib-induced ILD (organized pneumonia [OP]
78 pattern) was strongly suspected. Erlotinib was discontinued and 30 mg daily
79 prednisolone (PSL) was initiated. Symptoms and bilateral consolidations in the CT
80 improved, and PSL was gradually tapered to 5 mg (Fig. 1D).

81 After ~~cessation of erlotinib, he had received no treatment for 6 months because his~~
82 ~~lung cancer did not progress and he refused any further treatment. However, after 6~~
83 months without treatment, he had headache and impaired consciousness, and his

84 Eastern Cooperative Oncology Group performance status (ECOG PS) deteriorated to 2.
85 Cerebrospinal fluid (CSF) testing revealed the presence of malignant cells and he was
86 diagnosed with LM. He refused any cytotoxic chemotherapy; instead administration of
87 250 mg daily gefitinib and 4 mg daily betamethasone in addition to whole brain
88 radiotherapy was initiated. His symptoms and CSF test, however, worsened, and his
89 ECOG PS deteriorated to 4. The patient requested erlotinib retreatment despite the risk
90 of ILD, so we initiated administration of 150 mg daily erlotinib together with 4 mg
91 betamethasone. Soon after initiation of erlotinib, his symptoms dramatically improved
92 and ECOG PS improved to 1. Both his CSF test and brain magnetic resonance imaging
93 also improved (Fig. 2). His LM has not worsened for 8 months of erlotinib rechallenge.

94 During the period, betamethasone was gradually tapered to zero and ILD recurrence
95 has not been observed.

96

97 3. Literature review

98

99 In addition to the present case, a literature search identified a total of nine cases who
100 received EGFR-TKI retreatment after ILD induced by these drugs (Table 1) [17-24].

101 Three received gefitinib after gefitinib-induced ILD [17, 18, 24], 5 were treated with
102 erlotinib after gefitinib-induced ILD [19-22], and the remaining one (two including the
103 present case) received erlotinib after erlotinib-induced ILD [23]. Two patients were

104 Asians and the other reports were also from Asia, but the ethnicity of the patients was
105 not stated. Six patients were never-smokers and mMany had severe ILD as revealed by

106 bilateral diffuse ground glass opacities (GGO) on CT. ILD of all patients went into

107 remission on cessation of EGFR-TKIs and initiation of corticosteroid therapy. Two

108 patients (cases 2 and 10 in Table 1) could not be given any chemotherapy other than

109 EGFR-TKIs due to their poor PS. Although the others were fit enough to receive

110 chemotherapy, they requested EGFR-TKIs again instead. During the EGFR-TKI

111 rechallenge, only case 3 suffered recurrence of ILD. Seven patients were retreated with
112 a lower dose of EGFR-TKIs including case 3 who nonetheless recurred. In contrast,
113 cases 5, 6, and 10 had no recurrence in spite of receiving 150 mg daily erlotinib. Many
114 patients were given corticosteroids during EGFR-TKI rechallenge, but not case 3.
115 However; case 2 also received no corticosteroids but did not recur.

116

117 **4. Discussion**

118

119 In this article, we presented a case of successful erlotinib rechallenge for LM after
120 erlotinib-induced ILD and have summarized previous similar reports (Table 1).
121 Although nine of these ten cases successfully rechallenged with EGFR-TKIs without
122 the recurrence of ILD, most of the cases that do suffer recurrence might simply not be
123 reported. Therefore, the risk of ILD should be considered whenever reinitiating
124 EGFR-TKI treatment after ILD induced by these drugs. Eight of these ten cases could
125 have received other chemotherapies, but the patients requested EGFR-TKI therapy
126 again despite their awareness of the risk of ILD. This was permissible because the
127 efficacy of EGFR-TKIs was predicted from *EGFR* mutations or previous tumor

128 response. Our case (case 10 in Table 1) was not eligible for other chemotherapy due to
129 his poor PS, and the treatment of choice remained erlotinib or best supportive care.
130 Several cases in which LM resistant to gefitinib were improved by erlotinib due to its
131 higher CSF concentration have been reported [25-27] and ILD with an OP pattern on
132 CT seems to be associated with good prognosis [28]. Therefore, we used 150 mg daily
133 erlotinib because of its expected clinical benefit and efficacy despite the risk of ILD.
134 Seven patients were retreated with lower doses of EGFR-TKIs. Three received a
135 lower dose of erlotinib after gefitinib-induced ILD. However, the area under the curve
136 (AUC) of serum concentration of erlotinib at the approved dose (150 mg daily) is 7
137 times larger than gefitinib at the approved dose (250 mg daily) [29]. Therefore, in
138 spite of dose-reduction, higher AUC could be achieved by erlotinib than gefitinib in
139 these patients. In addition, case 3 had recurrence of ILD despite dose-reduction, and
140 three cases (cases 4, 5, and 10) had no recurrence of ILD although they received 150
141 mg daily erlotinib. From these findings, we speculate that blockade of the EGFR
142 signaling pathway by EGFR-TKIs is not necessarily associated with the occurrence of
143 ILD and that EGFR-TKI dose-reduction plays only a limited role in preventing
144 recurrence.

145 Dallas et al. have reported a similar case of successful erlotinib rechallenge after
146 erlotinib-induced ILD (case 9). As with the case reported here, that patient had also
147 received erlotinib retreatment together with corticosteroid after erlotinib-induced ILD.
148 Many cases were also given corticosteroids together with the EGFR-TKIs, resulting in
149 clinical benefit. In contrast, case 3 had recurrence of ILD without administration of
150 corticosteroid. This is consistent with the general use of corticosteroids for treating
151 drug-induced ILD [30, 31]. Thus, corticosteroid can prevent the recurrence of ILD,
152 probably because of its antiinflammatory action.

153 Six patients were never-smokers and CT finding of many patients revealed bilateral
154 diffuse GGO. We can predict the recurrence of ILD from these factors. In fact, a
155 previous report has shown that smoking status is one of the risk factors for ILD [14]. In
156 contrast, another report has shown that the incidence of the bilateral GGO pattern on
157 CT was relatively high and that such patients have high mortality rate [28]. Therefore,
158 great caution is required when undertaking rechallenge in these patients.

159 The mechanism responsible for ILD induced by EGFR-TKIs remains unclear and
160 several instances of successful EGFR-TKI rechallenge after ILD have been reported, as
161 described above. EGFR-TKIs are key drugs for patients with NSCLC having *EGFR*

162 mutations. Therefore, rechallenge after ILD should be undertaken considering the
163 balance between risk and benefit. This present case had an *EGFR* mutation and was not
164 eligible for other chemotherapy due to his poor PS. Therefore, the treatment of choice
165 remained erlotinib or best supportive care. Although he recognized the risk of ILD, he
166 requested erlotinib retreatment, and this was successful. From these findings, we
167 suggest 3 criteria before deciding on EGFR-TKI rechallenge after ILD; a) The patient
168 has an *EGFR* mutation. b) Few other treatment options except EGFR-TKI remain. c)
169 The patient recognizes the risk of ILD and makes an informed decision to go ahead
170 with the rechallenge. In order to assess the safety and the risk of this approach, more
171 similar cases including other ethnicities need to be accumulated and, if ethically
172 possible, prospective studies in patients who meet these criteria should be
173 performed~~are required~~.

174

175 **Conflict of interest statement**

176

177 None declared.

178 **References**

179

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308

309

310 **Figure Legends**

311

312 Figure 1. Chest computed tomography (CT) in a 68-year-old man. A: CT scan before
313 erlotinib treatment showing a mass in the left upper lobe. B, C: CT scan 10 weeks after
314 initiation of erlotinib treatment showing a decreased mass (B), but visible bilateral air
315 space consolidations (C). D: Eight weeks after cessation of erlotinib and initiation of
316 corticosteroid, showing improvement of the bilateral air space consolidations.

317

318 Figure 2. Brain magnetic resonance imaging (MRI). A: Contrast
319 (gadolinium)-enhanced T1-weighted MRI during gefitinib treatment before erlotinib
320 rechallenge, revealing leptomeningeal metastases (arrowheads). Patient performance
321 status (PS) had deteriorated to 4. B: Two weeks after the initiation of erlotinib, showing
322 improvement of the leptomeningeal metastases. PS also improved to 1.

Table 1. Patient characteristics

Case	Age (yr)	Sex	Ethnicity ^a	Histology	<i>EGFR</i> status	Smoking status	Onset of ILD	Cause of ILD (dose)	CT of ILD	Respiratory condition ^d	Treatment for ILD
1	62	F	NA	Ad	NA	Never	13 months	Gefitinib (125 mg/day ^b)	NA ^c	NA	Cessation and corticosteroid
2	56	M	NA	Ad	Exon 21; L858R	15 pack-year	45 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
3	59	M	NA	Ad	Wild type	60 pack-year	23 days	Gefitinib (250 mg/day)	Diffuse GGO	PaO ₂ , 46.9 mmHg	Cessation and corticosteroid
4	28	F	NA	Ad	Exon 19 deletion	Never	28 days	Gefitinib (250 mg/day)	Diffuse GGO	Need nasal oxygen	Cessation and corticosteroid
5	62	M	NA	Ad	Exon 19 deletion	18 pack-year	24 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
6	62	M	NA	Ad	NA	Never	6 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 84%	Cessation and corticosteroid
7	77	F	NA	Ad	NA	Never	7 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 93%	Cessation and corticosteroid
8	41	F	NA	Ad	NE	Never	20 days	Gefitinib (250 mg/day)	Patchy air space consolidation	PaO ₂ <45 mmHg	Cessation and corticosteroid
9	77	F	Asian	Ad	Exon 19 deletion	Never	5 weeks	Erlotinib (150 mg/day)	Diffuse GGO	Oxygen saturation, 92%	Cessation and corticosteroid
10	68	M	Asian	Ad	Exon 21; L858R	40 pack-year	8 weeks	Erlotinib (150 mg/day)	OP pattern	PaO ₂ , 78.6 mmHg	Cessation and corticosteroid

F, female; M, male; *EGFR*, epidermal growth factor receptor gene; ILD, interstitial lung disease; CT, computed tomography; GGO, ground glass opacity; OP, organized pneumonia; PaO₂, arterial oxygen pressure; NA, not available; NE, not evaluated.

^a The ethnicity of eight cases was not available, but all reports were from Asia.

^b Gefitinib was administered every other day due to blepharitis.

^c Case 1 had alveolar hemorrhage.

^d There was no description of actual PaO₂ or oxygen saturation in Cases 2, 4 and 5. But Cases 2 and 5 had severe ILD and Case 4 needed nasal oxygen supplementation (1 L/minute). Case 9 was supported by mechanical ventilation.

Table 1. Continued

Case	ECOG PS (symptoms)	Period between EGFR-TKIs	Rechallenge (dose)	Corticosteroid during rechallenge	Recurrence of ILD	Response of initial/rechallenge	References
1	1	12 months	Gefitinib (125 mg/day ^e)	NA	No	SD/SD	[17]
2	NA (Severe dyspnea and confined to bed)	5 months	Gefitinib (125 mg/day)	No	No	PR/PR	[18]
3	NA (General fatigue)	3 months	Gefitinib (Intermittent ^f)	No	Yes	NA	[19]
4	NA (Dyspnea)	4 months	Erlotinib (50 mg/day)	Yes → tapered	No	PR/PR	[20]
5	NA (Neurological symptoms)	3 months	Erlotinib (150 mg/day)	NA	No	NA/PR	[21]
6	NA	6 days	Erlotinib (150 mg/day)	Yes	No	PR/PR	[22]
7	NA	6 weeks	Erlotinib (100 mg/day)	Yes	No	PR/PR	[22]
8	NA	NA (about 6 months)	Erlotinib (75 mg/day)	Yes → off	No	PR/PR	[23]
9	NA	10 days	Erlotinib (100 mg/day)	Yes → off	No	PR/NA	[24]
10	4 (Impaired conscious)	7 months	Erlotinib (150 mg/day)	Yes → off	No	PR/PR	Present case

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; SD; stable disease; PR, partial response.

^e Gefitinib was administered every other day.

^f Gefitinib (250 mg daily) was administered for 7 days followed by 2 weeks rest.

Figure 1
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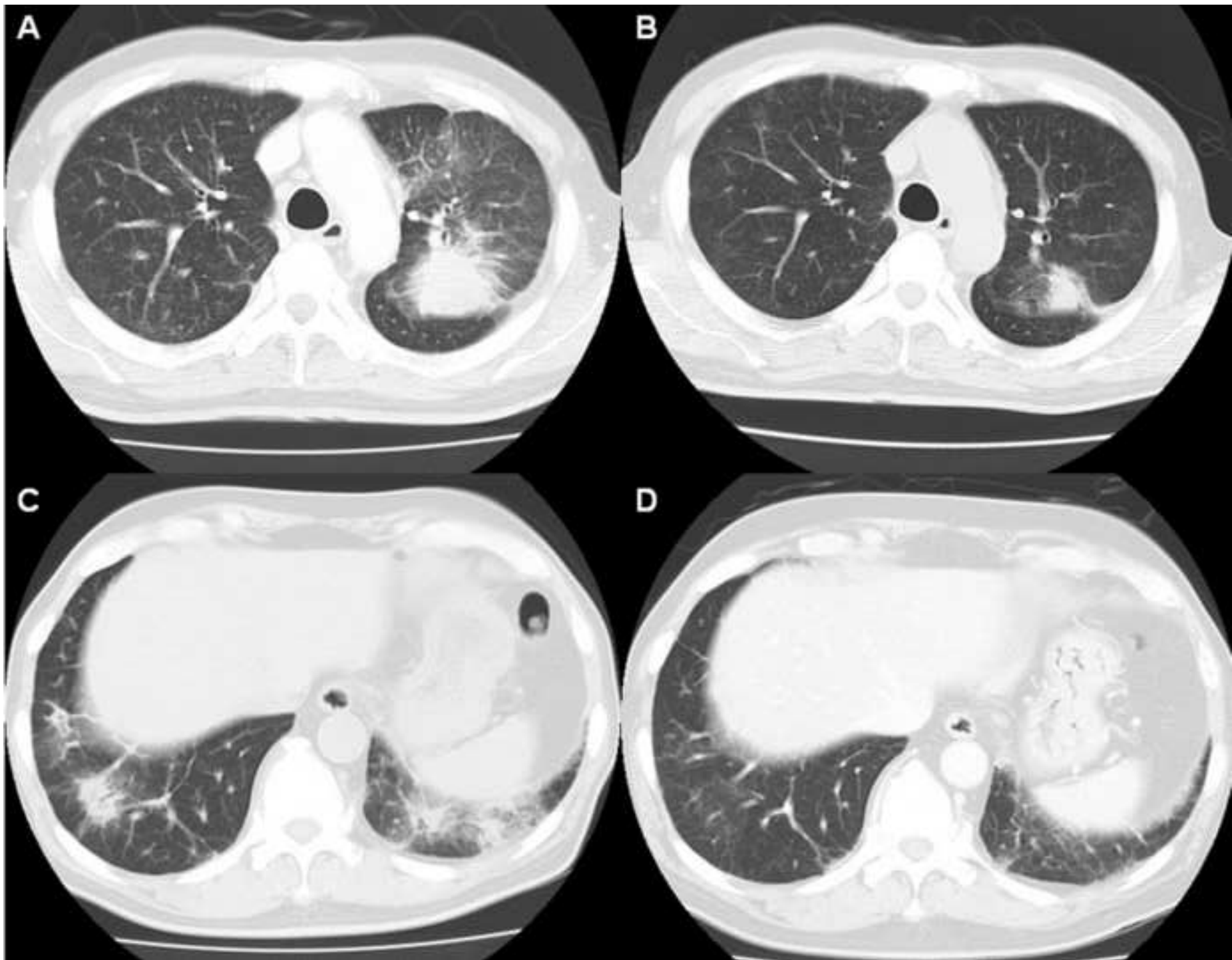


Figure 2
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