

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 September 26; 10(27): 9550-9969



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

September 26, 2022

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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# Drug-induced lung injury caused by acetaminophen in a Japanese woman: A case report

Masayoshi Fujii, Tsuneaki Kenzaka

**Specialty type:** Medicine, research and experimental

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Bao S, Australia; Jian X, China

**Received:** May 21, 2022

**Peer-review started:** May 21, 2022

**First decision:** June 27, 2022

**Revised:** July 2, 2022

**Accepted:** August 11, 2022

**Article in press:** August 11, 2022

**Published online:** September 26, 2022



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## Abstract

### BACKGROUND

All drugs have the potential to cause drug-induced lung injury both during and after drug administration. Acetaminophen has been reported to cause drug-induced lung injury, although this is extremely rare. Herein, we present an extremely rare case of acetaminophen-induced pneumonia.

### CASE SUMMARY

A healthy 35-year-old Japanese woman visited a neighborhood clinic with complaints of fever and malaise following a tick bite. Her treatment included 1,500 mg acetaminophen (Caronal®) and subsequently minocycline (200 mg) and acetaminophen (2,000 mg; Caronal®) daily when her condition did not improve; the patient was eventually hospitalized. The patient's chest computed tomography (CT) revealed consolidation and ground-glass opacities in the right middle and lower lobes. Minocycline was shifted to sulbactam/ampicillin. However, her fever did not improve during follow-up, and her chest CT revealed extensive ground-glass opacities in the right middle and lower lobes and thick infiltrative shadows in the bilateral basal areas. Drug-induced lung injury was suspected; hence, acetaminophen was discontinued. The fever resolved immediately, and inflammatory response and respiratory imaging findings improved. A drug-induced lymphocyte stimulation test was performed against acetaminophen (Caronal®), and significant proliferation of lymphocytes was noted only for acetaminophen (stimulation index, 2.1).

### CONCLUSION

Even common drugs such as over-the-counter drugs can cause drug-induced lung



damage.

**Key Words:** Acetaminophen; Computed tomography; Pneumonia; Fever; Tick bite; Case report

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**Core Tip:** We present an extremely rare case of acetaminophen-induced lung injury. Even common drugs, including over-the-counter drugs, can cause lung injury, warranting consideration when evaluating emergent lung disease.

**Citation:** Fujii M, Kenzaka T. Drug-induced lung injury caused by acetaminophen in a Japanese woman: A case report. *World J Clin Cases* 2022; 10(27): 9936-9944

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i27/9936.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i27.9936>

## INTRODUCTION

All drugs have the potential to cause drug-induced lung injury both during and after drug administration. Although this is extremely rare, acetaminophen can also reportedly cause drug-induced lung injury[1]. Drug-induced lung disease is associated with various pathophysiologic and clinical presentations and syndromes. However, certain clinical patterns of pneumonia are likely to occur with specific types of drugs, as previously reported[2]. The drug provocation test is the gold standard for confirming the diagnosis of drug hypersensitivity[3]. However, this test is associated with a high risk of severe side effects; therefore, its use is controversial.

In clinical practice, resolution of symptoms after suspected drug exposure cessation is usually sufficient for diagnosis without the need for rechallenge[4]. The diagnosis of drug-induced lung injury is based on a combination of information, including symptoms, physical examinations, drug intake and medical history, and imaging and pathological findings[5]. Acetaminophen-induced lung injury generally presents as a clinical form of drug-induced eosinophilic pneumonia[1,2]. Acetaminophen is one of the most frequently used drugs, and a few studies have reported acetaminophen-induced lung injury. Herein, we describe the clinical characteristics of acetaminophen-induced pneumonia in a Japanese woman.

## CASE PRESENTATION

### Chief complaints

A healthy 35-year-old Japanese woman visited a neighborhood clinic 7 d before hospitalization with complaints of fever and malaise.

### History of present illness

She was bitten by a tick while cleaning her house 9 d before hospitalization.

### History of past illness

Nothing in particular.

### Personal and family history

Her personal and family history was unremarkable. On admission, she had no history of smoking or allergies as well.

### Physical examination

On physical examination at admission, the patient's temperature was 37.3 °C, blood pressure was 93/52 mmHg, pulse rate was 72 beats/min, respiration rate was 16 breaths/min, and peripheral capillary oxygen saturation level was 96% (room air).

Respiratory and cardiovascular tests yielded clear results. Lymph nodes were palpable in the right axilla with two erythematous patches in the surrounding area.

### Laboratory examinations

The patient's peripheral white blood cell count was 8310/mm<sup>3</sup>, with 86.5% neutrophils, 11.7% lymphocytes, and 0.0% eosinophils. Her C-reactive protein level was 31.65 mg/dL. Tests for antibodies against *Orientia tsutsugamushi* showed negative findings. Blood culture results were also negative. Urine culture revealed *Enterococcus species* and coagulase-negative *Staphylococci* (Table 1).

### Imaging examinations

Chest radiography revealed interstitial shadows in the right lower lung (Figure 1A). Physical examination revealed a palpable right axillary lymph node; therefore, thoracoabdominal computed tomography (CT) was performed for deep lymph node evaluation. Chest CT revealed consolidation and ground-glass opacities in the right middle and lower lobes (Figure 2A). Minocycline was discontinued because of the low risk of rickettsial infection. Acetaminophen (Caronal®) 2000 mg was administered orally, and acetaminophen (Acelio®) 500 mg was administered intravenously for symptomatic treatment.

## FURTHER DIAGNOSTIC WORK-UP

We suspected pyelonephritis; based on the antimicrobial susceptibility of urine culture results, we administered sulbactam/ampicillin 3 g every 6 h for 3 d. However, a fever of > 38 °C persisted. On day 4 of hospitalization, repeat chest radiography revealed worsening of interstitial shadows in the right lower lung (Figure 1B), and chest CT revealed extensive ground-glass opacities mainly in the right middle and lower lobes and thick infiltrative shadows in the bilateral basal areas. In addition, thickening of the interlobular septum, bronchovascular bundles, and bilateral pleural effusions suggested eosinophilic pneumonia or organizing pneumonia (Figure 2B and C).

## FINAL DIAGNOSIS

We suspected atypical pneumonia or interstitial pneumonia and investigated the patient for infections and collagen diseases; however, serological tests for common causative agents of atypical pneumonia and autoimmune disease-associated autoantibodies revealed negative results (Table 1).

## TREATMENT

The patient was treated with acetaminophen 1500 mg (Caronal®); however, her condition did not improve. Three d before hospitalization, she presented with a fever of 38 °C and a lack of appetite. We suspected rickettsial infection at this time and initiated daily administration of minocycline (200 mg) and acetaminophen (2,000 mg; Caronal®); however, her condition did not improve; therefore, she was admitted to our hospital.

Atypical pneumonia was considered in the differential diagnosis, and azithromycin 500 mg was administered as the first dose, followed by 250 mg every 24 h for 5 d after the second dose. Since we suspected drug-induced lung injury, acetaminophen was discontinued and replaced with a nonsteroidal anti-inflammatory drug, resulting in resolution of fever on day 6 of hospitalization and improvement in inflammatory response and pulmonary imaging findings, without immunosuppressive or anti-inflammatory therapy, on day 10 of hospitalization (Figure 2D). Hypoxemia was not observed during hospitalization; therefore, the drug was discontinued, and the patient was discharged on day 13 of hospitalization. The drug-induced lymphocyte stimulation test (DLST) was performed against acetaminophen (Caronal®) and minocycline post-discharge, and negative results were obtained for minocycline, with significant proliferation of lymphocytes noted only for acetaminophen and a stimulation index of 2.1. The sensitivity of the DLST is reported to be 60%-70%, and its specificity is 85%; however, false-positive results have also been reported; therefore, the DLST was only intended to assist the diagnostic process [6,7].

## OUTCOME AND FOLLOW-UP

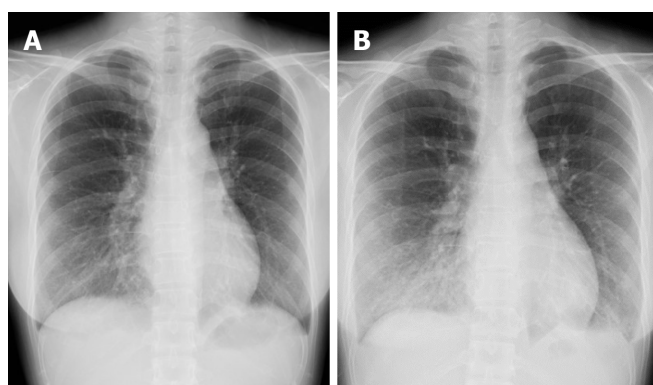
The diagnostic criteria for drug-induced lung injury outlined by Camus *et al* [2] are as follows: (1) Correct identification of the drug; (2) Singularity of the drug; (3) Temporal eligibility; (4) Characteristic clinical, imaging, bronchoalveolar lavage, and pathologic patterns of reaction to the specific drug; and (5) Exclusion of other causes of interstitial lung disease (ILD). The patient was healthy, had no history of ILD, and had a new history of acetaminophen and minocycline exposure. Minocycline was

**Table 1 Laboratory and serological test findings representative of atypical or interstitial pneumonia at admission**

Parameter	Recorded value	Standard range
White blood cell count	8310/ $\mu$ L	4500-7500/ $\mu$ L
Neutrophil	86.50%	
Lymphocyte	11.70%	
Monocyte	1.70%	
Eosinophils	0.00%	
Hemoglobin	11.8 g/dL	11.3-15.2 g/dL
Platelet count	$23.2 \times 10^3$ / $\mu$ L	$13-35 \times 10^3$ / $\mu$ L
Total protein	6.9 g/dL	6.9-8.4 g/dL
Albumin	3.5 g/dL	3.9-5.1 g/dL
Total bilirubin	0.7 mg/dL	0.2-1.2 mg/dL
Aspartate aminotransferase	31 U/L	11-30 U/L
Alanine aminotransferase	26 U/L	4-30 U/L
Lactate dehydrogenase	368 U/L	109-216 U/L
Blood urea nitrogen	9.6 mg/dL	8-20 mg/dL
Creatinine	0.5 mg/dL	0.63-1.03 mg/dL
Sodium	135 mEq/L	135-145 mEq/L
Potassium	4.2 mEq/L	3.6-5.2 mEq/L
Chlorine	98 mEq/L	98-108 mEq/L
C-reactive protein	31.65 mg/L	$\leq 1.0$ mg/L
Procalcitonin	0.66 ng/mL	$\leq 0.3$ ng/mL
KL-6	205 U/mL	$\leq 500$ U/mL
Surfactant protein A	105.9 ng/mL	$\leq 43.8$ ng/mL
Surfactant protein D	105.3 ng/mL	$\leq 110$ ng/mL
C3	136 mg/dL	86-160 mg/dL
C4	28.7 mg/dL	17-45 mg/dL
IgG	1137 mg/dL	870-1700 mg/dL
IgA	193 mg/dL	110-410 mg/dL
IgM	134 mg/dL	35-220 mg/dL
ACE	15.2 U/mL	8.3-21.4 U/mL
Antinuclear antibody	< 40	< 40
RF	< 3 U/mL	0-15 U/mL
Anti-CCP antibody	0.8 U/mL	< 5 U/mL
Anti-Ro/SS-A antibody	Negative	Negative
Anti-La/SS-B antibody	Negative	Negative
Anti-Jo-1 antibody	Negative	Negative
Anti-ARS antibody	Negative	Negative
PR3-ANCA	Negative	Negative
MPO-ANCA	Negative	Negative
<i>Orientia tsutsugamushi</i> Karp IgG	< 10	< 10
<i>Orientia tsutsugamushi</i> Karp IgM	< 10	< 10
<i>Orientia tsutsugamushi</i> Kato IgG	< 10	< 10

<i>Orientia tsutsugamushi</i> Kato IgM	< 10	< 10
<i>Orientia tsutsugamushi</i> Gilliam IgG	< 10	< 10
<i>Orientia tsutsugamushi</i> Gilliam IgM	< 10	< 10
<i>C. pneumoniae</i> IgG	Negative	Negative
<i>C. pneumoniae</i> IgA	Negative	Negative
CMV-IgG	199.7	0.0-1.0
CMV-IgM	< 0.85	0-0.7
<i>M. pneumoniae</i> PCR of the sputum	Negative	Negative
Urine Legionella antigen testing	Negative	Negative
Beta-D-glucan assay	9.0 pg/mL	
Aspergillus IgG	Negative	Negative
Anti- <i>Trichosporon asahii</i> antibody	Negative	Negative

ACE: Angiotensin I-converting enzyme; ANCA: Antineutrophil cytoplasmic antibodies; ARS: Aminoacyl tRNA synthetase; *C. pneumoniae*: *Chlamydia pneumoniae*; CCP: Cyclic citrullinated peptide; CMV: Cytomegalovirus; Ig: Immunoglobulin; KL-6: Sialylated carbohydrate antigen KL-6; *M. pneumoniae*: *Mycoplasma pneumoniae*; MPO: Myeloperoxidase; PCR: Polymerase chain reaction; PR3: Proteinase 3; RF: Rheumatoid factor.



DOI: 10.12998/wjcc.v10.i27.9936 Copyright ©The Author(s) 2022.

**Figure 1** Chest radiography images. A: Chest radiography at admission shows right lower lung interstitial shadows; B: Chest radiography on day 4 of hospitalization shows worsened right lower lung interstitial shadows.

administered for 3 d and discontinued on admission. The patient developed drug-induced eosinophilic pneumonia-like imaging findings on day 4 of hospitalization. The imaging findings worsened gradually after discontinuation of minocycline until day 4 of hospitalization, suggesting that minocycline was unlikely to have influenced the patient's disease. On the other hand, symptoms and imaging findings rapidly improved after discontinuation of acetaminophen on day 4 of hospitalization. In addition, other potential causes of ILD, such as infections and collagen diseases, were excluded. Although the drug provocation test was not performed, all diagnostic criteria were met, and acetaminophen-induced pneumonia was diagnosed. No recurrence of ILD was observed in the last 4 years since the patient first visited our clinic.

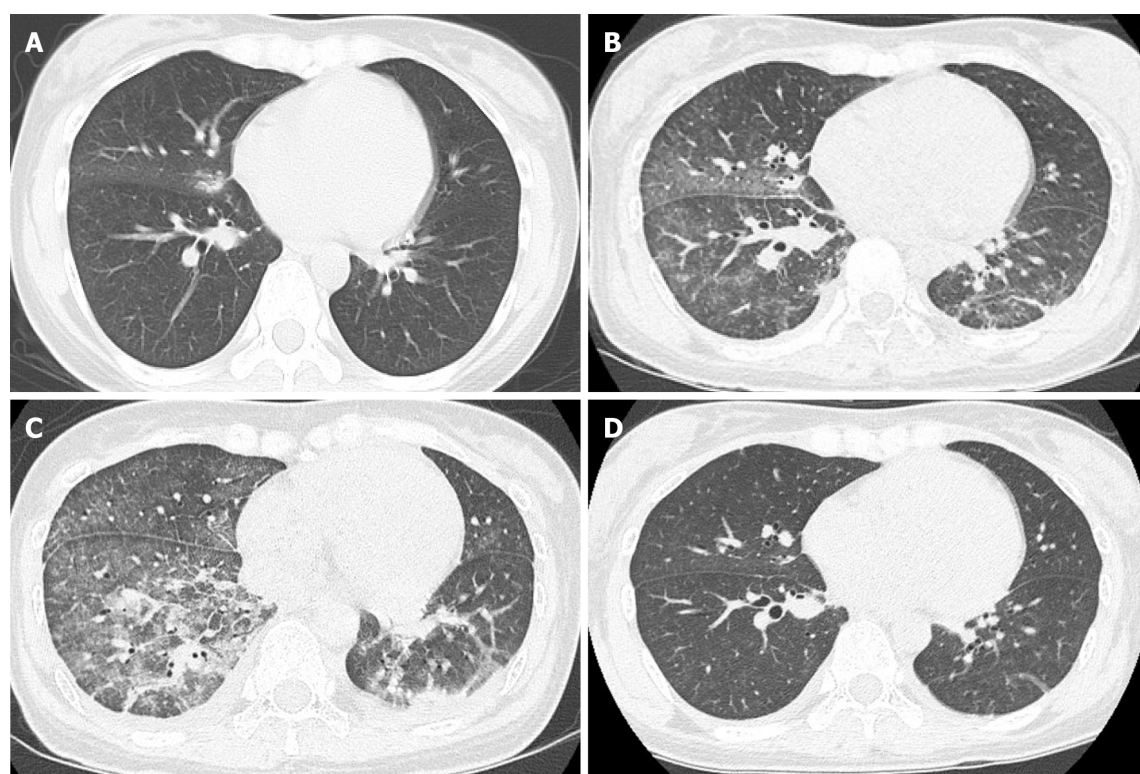
## DISCUSSION

We present an extremely rare case of acetaminophen-induced lung injury. Although the drug provocation test was not performed in this case, we diagnosed acetaminophen-induced lung injury based on the history of drug administration, clinical course, and DLST results. The imaging findings suggested eosinophilic pneumonia; however, since bronchoalveolar lavage was not performed, the diagnosis could not be confirmed. Acetaminophen is an extremely rare causative agent of drug-induced pneumonia[1,2,8,9]. Acetaminophen-induced lung injury has been reported in 16 patients, excluding the patient in this case, as indexed in PubMed (Table 2)[10-24]. Among the 17 patients, including our patient, 12 (70.6%) were female patients, five (29.4%) were male patients, and 16 (94.1%) were Japanese patients. Only one case of a Caucasian patient has been reported in another country. The patients'

Table 2 Clinical characteristics of patients with reported acetaminophen-induced lung injury

Case	Sex	Age (years)	Ethnicity	Drugs	Symptoms	Time between drug use and presentation (d)	Time between initial diagnosis and drug discontinuation (d)	Treatment	Outcome	Ref.
1	Female	20	Japanese	Acetaminophen (Norshin <sup>®</sup> )	Fever, cough, and dyspnea	2	0	Drug discontinuation; Corticosteroids	Disease resolution	Kitaguchi <i>et al</i> [10], 1992
2	Female	63	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Cough and dyspnea	8	10	Drug discontinuation; Corticosteroids	Disease resolution	Kudeken <i>et al</i> [11], 1993
3	Male	45	Japanese	Acetaminophen (PL Combination Granules <sup>®</sup> )	Fever, cough, and diarrhea	4	0	Drug discontinuation	Disease resolution	Nakatsumi <i>et al</i> [12], 1994
4	Male	75	Japanese	Acetaminophen (Pabron gold <sup>®</sup> /Pabron S <sup>®</sup> )	Fever and dyspnea	3	0	Drug discontinuation; Corticosteroids	Disease resolution	Nomura <i>et al</i> [13], 1997
5	Male	57	Japanese	Acetaminophen (PL Combination Granules <sup>®</sup> /Shin Lulu A Tablets <sup>®</sup> )	Fever, cough, and dyspnea	11	8 months	Drug discontinuation; Corticosteroids	Respiration and disease resolution	Kawano <i>et al</i> [14], 1997
6	Female	64	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Fever, cough, and dyspnea	19	8	Drug discontinuation; Corticosteroids	Disease resolution	Akashi <i>et al</i> [15], 1997
7	Female	70	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Fever, cough, and dyspnea	6	5	Drug discontinuation; Corticosteroids	Disease resolution	Nakajima <i>et al</i> [16], 1998
8	Female	49	Japanese	Acetaminophen (Benza Block SP <sup>®</sup> )	Fever and dyspnea	5	5	Drug discontinuation; Corticosteroids	Disease resolution	Nakajima <i>et al</i> [16], 1998
9	Male	72	Japanese	Acetaminophen (PL Combination Granules <sup>®</sup> )	Fever and dyspnea	1	0	Drug discontinuation; Corticosteroids	Respiration and Disease resolution	Ikeuchi <i>et al</i> [17], 2000
10	Male	31	Japanese	Acetaminophen (PL Combination Granules <sup>®</sup> )	Fever and cough	13	31	Drug discontinuation	disease resolution	Hiramatsu <i>et al</i> [18], 2002
11	Female	68	Japanese	Acetaminophen (PL Combination Granules <sup>®</sup> )	Fever, cough, and dyspnea	6	0	Drug discontinuation; Corticosteroids, Cyclosporine	Disease resolution	Nakayama <i>et al</i> [19], 2006
12	Female	41	Japanese	Acetaminophen (Ibuprofen <sup>®</sup> /Caronal <sup>®</sup> )	Fever, cough, and dyspnea	3	0	Drug discontinuation; Corticosteroids	Disease resolution	Anan <i>et al</i> [20], 2009
13	Female	84	Japanese	Acetaminophen (Shin Lulu A Tablets s <sup>®</sup> )	Fever, cough, and dyspnea	5	0	Drug discontinuation; Corticosteroids	Disease resolution	Kato <i>et al</i> [21], 2010
14	Female	80	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Fever and dyspnea	15	0	Drug discontinuation; Corticosteroids	Disease resolution	Sasaki <i>et al</i> [22], 2014
15	Female	68	Caucasian	Acetaminophen (Caronal <sup>®</sup> )	Cough and dyspnea	Months	Not specified	Drug discontinuation	Disease resolution	Saint-Pierre <i>et al</i> [23], 2016
16	Female	79	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Dyspnea	2	0	Drug discontinuation; Corticosteroids	Disease resolution	Ueda <i>et al</i> [24], 2019
Present case	Female	35	Japanese	Acetaminophen (Caronal <sup>®</sup> )	Fever	4	11	Drug discontinuation	Disease resolution	-





DOI: 10.12998/wjcc.v10.i27.9936 Copyright ©The Author(s) 2022.

**Figure 2 Chest computed tomography images.** A: Chest computed tomography at admission reveals right middle and lower lobar consolidation and ground-glass opacity; B and C: Chest computed tomography on day 4 of hospitalization shows extensive ground-glass opacity, mainly in the right middle and lower lobes, and thick bilateral basal infiltrative shadows. In addition, thickening of the interlobular septum and bronchovascular bundles, and bilateral pleural effusion, suggestive of eosinophilic or organizing pneumonia, are seen; D: Chest computed tomography on day 10 of hospitalization shows improvement of ground-glass opacity and infiltrative shadows.

median age was 64 years (interquartile range [IQR], 45-72 years). Acetaminophen and over-the-counter drugs containing acetaminophen were the causative agents in nine (52.9%) and eight (47.1%) patients, respectively. Seven (41.1%) patients met the diagnostic criteria for drug-induced eosinophilic pneumonia[1,8]. The median time (in d) between drug exposure and the onset of respiratory symptoms was 5 d (IQR, 3-11 d); the onset was often relatively short-lived after the initiation of medication. In all patients, the causative drug was discontinued at the start of treatment, and the condition of four (23.5%) patients improved with discontinuation of the drug alone, while 13 (76.5%) patients required corticosteroids. Two patients required ventilation management, and all patients were discharged with good outcomes.

There are several reasons for the relatively high number of reports of acetaminophen-induced lung injury in Japan. First, racial differences may exist, such that drug-induced lung injury has been associated with ethnicity. The incidence and mortality rates of drug-induced lung injuries are higher in Japan than in other countries[5]. These ethnicity-based differences suggest possible variations in the genes related to lung fragility in Japanese patients[25]. The *MUC4* gene is suspected to be the causative gene and remains under investigation. Furthermore, a large number of CT examinations than those performed in other countries[26] may affect these rates.

Several drugs can induce lung injury both during and after administration[2]. Acetaminophen is a frequently prescribed drug in clinical practice and is a constituent of many medical and over-the-counter drugs. The incidence of drug-induced lung injury has been reported for acetaminophen alone and for acetaminophen-containing combination drugs and over-the-counter drugs. In previous reports, eight (47.1%) patients were suspected of having acetaminophen-induced lung injury at the time of initial diagnosis, and the drug was discontinued[24]. The eight patients, including the patient in this case, were not diagnosed with acetaminophen-induced lung injury at the time of initial diagnosis and continued to use it. Acetaminophen is not easily identified as a cause of drug-induced lung injury because of the rarity of the injury and the tendency of patients to withhold information on frequently or recently used drugs. In many cases, patients recover spontaneously on discontinuing the drug; however, a severe course is noted in some cases. Therefore, in this case, acetaminophen should have been discontinued at an early stage. It is important to remember that even common drugs, including over-the-counter drugs, can cause drug-induced lung injury.

## CONCLUSION

We have presented an extremely rare case of acetaminophen-induced lung injury. Even common drugs, including over-the-counter drugs, can cause lung injury and must be considered when evaluating emergent lung disease.

## FOOTNOTES

**Author contributions:** Fujii M managed the case and revised and corrected the manuscript; Kenzaka T assisted with redaction, correction, and reconstruction of the manuscript; all authors read and approved the final manuscript.

**Informed consent statement:** The patient provided written informed consent for the publication of this case report and accompanying images. A copy of the consent form is available for review by the editor of this journal.

**Conflict-of-interest statement:** All authors declare that they have no conflict of interest to disclose.

**CARE Checklist (2016) statement:** All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**S-Editor:** Wang LL

**L-Editor:** A

**P-Editor:** Wang LL

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