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Case report

Unilateral methotrexate-induced lung injury with foreign bodies in the airway: A case report

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ABSTRACT

A 75-year-old woman who had been taking methotrexate presented to our hospital for fever and dry cough. Chest computed tomography showed ground-glass opacity in the upper lobe of the right lung and foreign bodies in the lower lobe of the right bronchus. During bronchoscopy, foreign bodies were removed from the airway. We found increased levels of lymphocytes and a high CD4/CD8 ratio in the bronchoalveolar lavage fluid. Transbronchial lung biopsy revealed lymphocytic infiltration. Methotrexate was discontinued, and the imaging findings improved. Methotrexate-induced lung injury does occur unilaterally. Foreign bodies in the airway might also trigger unilateral methotrexate-induced lung injury.

1. Introduction

Methotrexate (MTX) is used for rheumatoid arthritis and for leukemia, as well as other malignancies. MTX-induced lung injury (MTX-ILI) is a widely known adverse event. Like other drug-ILIs, almost all cases of MTX-ILI manifest radiologically with shadows in both lungs [1]. Unilateral drug-ILI has been very rare; it was often clinically diagnosed due to inadequate examinations in the past. Drug-ILI is difficult to diagnose because no diagnostic method is specific to this condition, and whether drug-ILI can be unilateral has been unclear. Also, drug-ILI with concomitant foreign bodies in the airways has not been described previously. We report a case of unilateral MTX-ILI in which adequate examination was performed, and the radiological lung shadow improved only after discontinuation of MTX. In our patient, unilateral MTX-ILI occurred after aspiration of foreign bodies. We describe the relationship between unilateral drug-ILI and foreign bodies in the airways and review the related literature.

2. Case presentation

A 75-year-old woman had been taking MTX for 2 years for rheumatoid arthritis. She presented with a fever and a dry cough that had started after dinner. The next day, a chest x-ray showed a ground-glass opacity in the right upper lung field (Fig. 1A). A general

Abbreviations: MTX, methotrexate; ILI, induced lung injury; CT, computed tomography; KL-6, Krebs von den Lungen 6; C7HRP, cytomegalovirus pp65 antigen; T-SPOT.TB, tuberculosis-specific interferon- γ ; DLST, drug lymphocyte stimulation test; BALF, bronchoalveolar lavage fluid.

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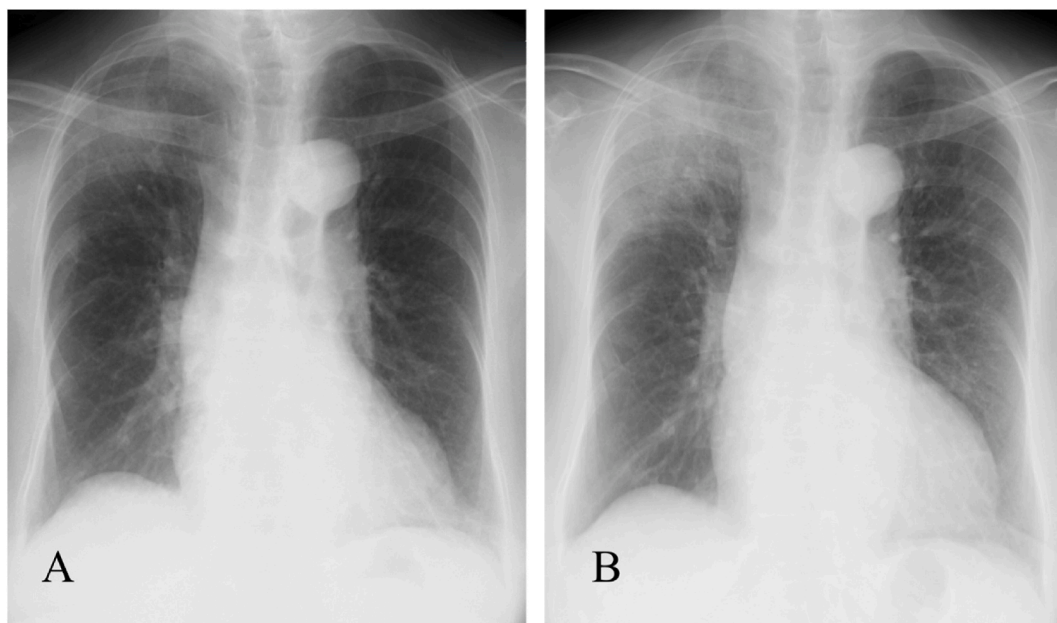


Fig. 1. Chest x-rays showing an enlarged ground-glass opacity in the right upper lung field. (A) 5 days before hospital admission. (B) The day of hospital admission.

Table 1

Results of laboratory tests on hospital admission.

Hematologic findings			Serologic findings			BALF results (right lung B ³)		
WBC count	6000	/μL	C-reactive protein	14.0	mg/dL	Recovery	86/150	mL
Neutrophils	86.7	%	IgG	1324	mg/dL	WBC count	3.8×10^5	/mL
Lymphocytes	7.6	%	IgA	192	mg/dL	Neutrophils	4	%
Monocytes	5.0	%	IgM	66	mg/dL	Lymphocytes	35	%
Eosinophils	0.5	%	50% complement activity	65	IU/mL	Eosinophils	3	%
Basophils	0.2	%	Rheumatoid factor	9	IU/mL	Macrophages	58	%
RBC count	363	$\times 10^4/\mu\text{L}$	Antinuclear antibodies	<40	×	CD4/CD8	4.62	
Hemoglobin	11.3	g/dL	Proteinase 3 ANCA	<10	U/mL	Culture	–	
Hematocrit	33.7	%	Myeloperoxidase ANCA	<10	U/mL	TB PCR	–	
Platelet count	27.0	$\times 10^4/\mu\text{L}$	KL-6	269	U/mL	MAC PCR	–	
			Surfactant protein D	149	ng/mL			
			B-type natriuretic peptide	57.3	pg/mL			
			<i>Mycoplasma pneumoniae</i> Ab	<40	×	DLST		
			2 weeks later	<40	×	Methotrexate	+	
Biochemistry findings			<i>Chlamydia pneumoniae</i> IgM	0.29				
Total protein	7.0	g/dL	<i>C. pneumoniae</i> IgA	2.90				
Albumin	3.3	g/dL	<i>C. pneumoniae</i> IgG	2.21				
Total bilirubin	0.5	mg/dL	<i>Chlamydia psittaci</i> Ab	–		Blood culture	–	
Aspartate aminotransferase	24	IU/L	<i>Candida</i> antigen	–		Sputum culture	Normal	flora
Alanine aminotransferase	15	IU/L	<i>Aspergillus</i> antigen	–				
γ -Glutamyl transpeptidase	29	IU/L	<i>Cryptococcus</i> antigen	–				
Alkaline phosphatase	286	IU/L	β -D-glucan	–				
Lactate dehydrogenase	246	IU/L	CMV pp65 antigen C7HRP	–				
Blood urea nitrogen	22.2	mg/dL	T-SPOT.TB test	–				
Creatinine	0.52	mg/dL						
Sodium	133	mEq/L	Urinary antigen					
Potassium	4.7	mEq/L	<i>Streptococcus pneumoniae</i>	–				
Chlorine	95	mEq/L	<i>Legionella pneumophila</i>	–				
Fasting blood glucose	105	mg/dL						
Hemoglobin A1c	4.8	%						

WBC, white blood cell; RBC, red blood cell; Ig, Immunoglobulin; ANCA, antineutrophil cytoplasmic antibodies; KL-6, Krebs von den Lungen 6; Ab, antibody; PCR, polymerase chain reaction; CMV, cytomegalovirus; TB, tuberculosis; MAC, *Mycobacterium avium*–*Mycobacterium intracellulare* complex; BALF, bronchoalveolar lavage fluid; DLST drug lymphocyte stimulation test.

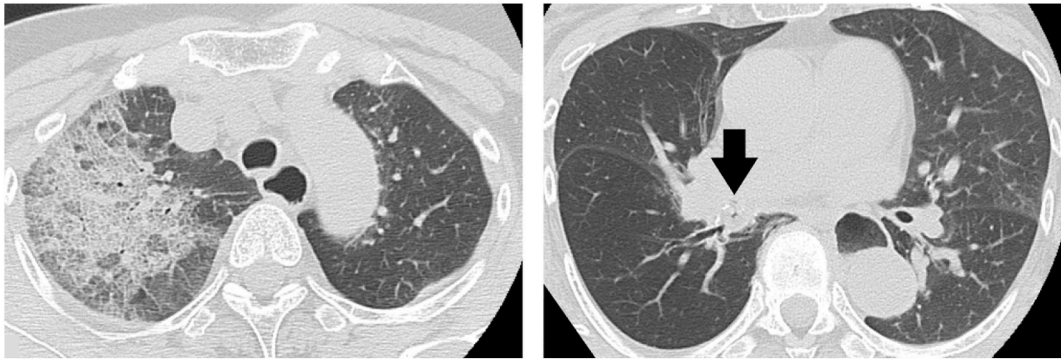


Fig. 2. Chest CT showing a ground-glass opacity in the upper lobe of the right lung and foreign bodies in the lower lobe of the right bronchus (arrow).

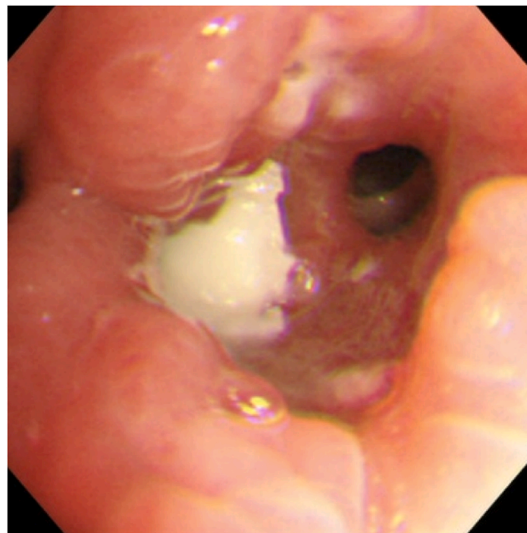


Fig. 3. Bronchoscopic view showing white foreign bodies in the basal segment of the right bronchus.

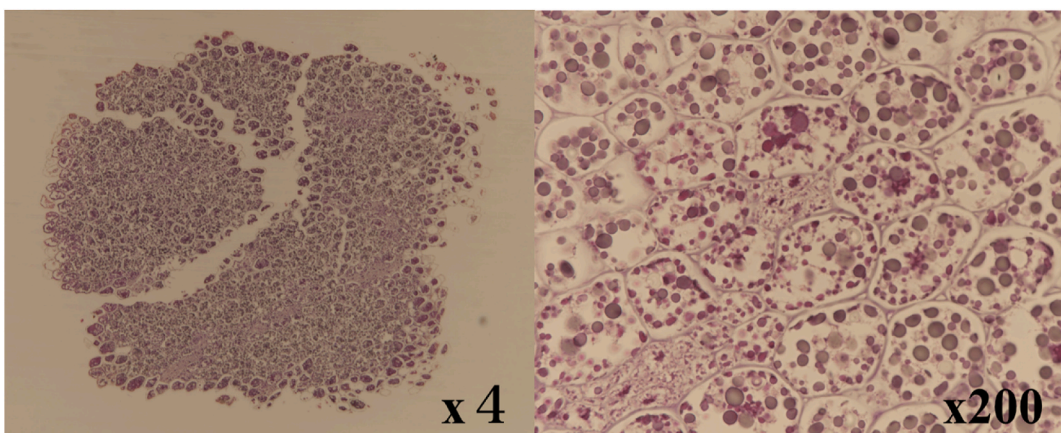


Fig. 4. Foreign bodies in the airway. Inside the dense cluster of chamber-like structures surrounded by wall-like structures, a small number of eosinophilic spherical structures are found. Plant seeds are suspicious but are difficult to identify due to the lack of shells.

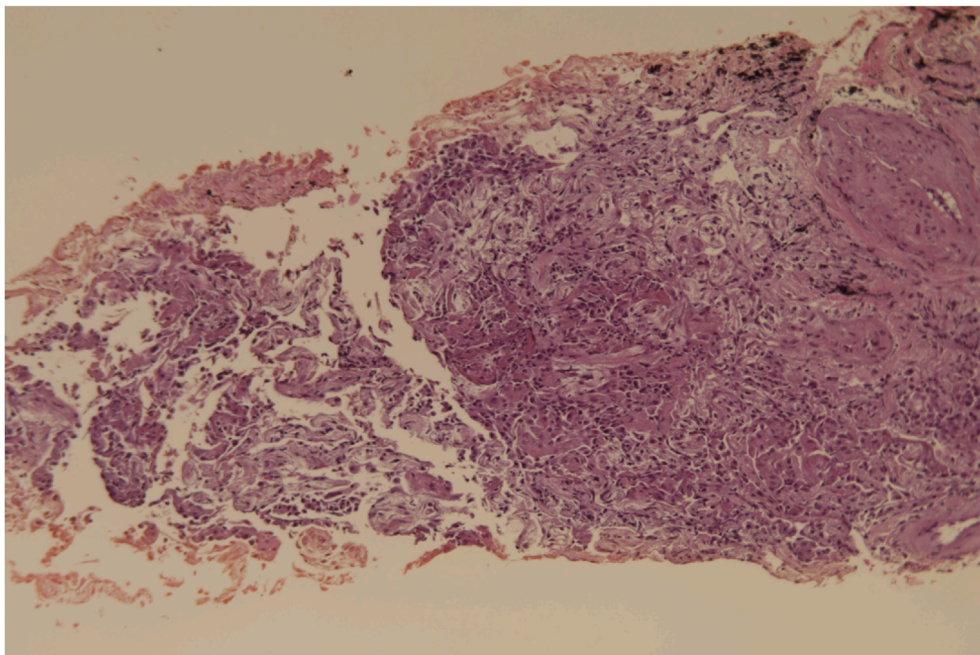


Fig. 5. Transbronchial biopsy specimen shows lymphocytic infiltration and fibrous thickening of the septum (hematoxylin and eosin stain).



Fig. 6. Contrast-enhanced chest CT on the 26th day shows only a slight scar in the upper lobe of the right lung and no blood flow disruption. The methotrexate has only been discontinued. Following a discontinuity of methotrexate, the ground-glass opacity in the right upper lung field has gradually disappeared.

practitioner diagnosed that she had a *Mycoplasma pneumoniae* infection, and she was prescribed clarithromycin, 400 mg/day.

Five days later, because the fever and dry cough persisted, she was admitted to our hospital. Physical examination revealed a temperature of 38.0 °C, a respiratory rate of 20/minute, and room-air oxygen saturation of 96%. Fine crackles were heard in the right anterior part of the chest. A chest x-ray showed an enlarged ground-glass opacity in the right upper lung field (Fig. 1B).

Laboratory tests revealed a C-reactive protein level of 14.0 mg/dL, a Krebs von den Lungen 6 (KL-6) level of 269 U/mL, and a surfactant protein D level of 149 ng/mL. Crucial findings were that *Mycoplasma pneumoniae* antibody, *Chlamydomphila pneumoniae* immunoglobulin M, *Chlamydomphila psittaci* antibody, *Legionella pneumophila* antigen, *Streptococcus pneumoniae* antigen, β -D-glucan, *Candida* antigen, *Aspergillus* antigen, *Cryptococcus* antigen, and cytomegalovirus pp65 antigen C7HRP (cytomegalovirus antigenemia) were not present, and results of the T-SPOT.TB test (tuberculosis-specific interferon- γ) and blood cultures were all negative. The drug lymphocyte stimulation test (DLST) yielded positive results for MTX (Table 1).

Chest computed tomography (CT) showed a ground-glass opacity in the upper lobe of the right lung and foreign bodies in the lower

Table 2
Clinical characteristics of all reported cases of unilateral drug-induced lung injury.

Case no.	Age, sex	Drug	Background	CT findings	BALF findings	TBLB findings	Reference
1	54, F	Methotrexate	Squamous cell lung carcinoma	–	–	Inflammatory cell infiltration Fibrous thickening of the septum	2
2	71, M	Amiodarone	Ventricular tachycardia	–	Mild increase in neutrophils	Nonspecific inflammation	8
3	78, M	Amiodarone	Ventricular tachycardia	Consolidation	Mild increase in neutrophils	Organizing pneumonia	9
4	44, F	Balsalazide	Ulcerative colitis	Consolidation Opacity	–	Eosinophilic pneumonia	10
5	53, F	Mesalamine	Ulcerative colitis	–	Increase in eosinophils	Eosinophilic pneumonia	11
6	49, F	Nivolumab	Endometrial cancer	Opacity	Neutrophils and lymphocytes	–	12
7	76, M	Loxoprofen	Lung adenocarcinoma (postoperative finding)	Opacity	Increase in eosinophils	–	13
8	74, F	Meropenem	Lung adenocarcinoma (postoperative finding)	Consolidation Opacity	Increase in eosinophils	–	14
9	81, F	Fibrin sealant	Lung adenocarcinoma (postoperative finding)	Opacity	Increase in eosinophils	–	15
10	73, M	Ampicillin/sulbactam	Mycoplasma pneumonia	–	–	–	16
11	54, F	Sirolimus	Cadaveric renal transplantation	Consolidation Opacity	Mild increase in neutrophils	Organizing pneumonia	17
12	53, M	Mitomycin Vindesine Cisplatin	Squamous cell lung carcinoma	Opacity	–	–	18
Our patient	75, F	Methotrexate	Rheumatoid arthritis Airway foreign bodies	Opacity	Increase in lymphocytes	Lymphocytic infiltration Fibrous thickening of the septum	

CT, computed tomography; BALF, bronchoalveolar lavage fluid; TBLB, transbronchial lung biopsy.

lobe of the right bronchus (Fig. 2).

A bronchoscopy revealed white foreign bodies in the right bronchus basal segment, which we removed with biopsy forceps (Fig. 3).

Pathological examination demonstrated a small number of eosinophilic spherical structures inside a dense cluster of chamber-like structures surrounded by wall-like structures. We suspected that the spherical structures represented some plant seed, but it was difficult to identify because of the lack of shells (Fig. 4).

Bronchoalveolar lavage fluid (BALF) from the right lung B³ showed a total cell count of 3.8×10^5 /mL (4% neutrophils, 35% lymphocytes, 3% eosinophils, 58% macrophages, and a CD4/CD8 ratio of 4.62), and cultures of BALF yielded negative results. Transbronchial lung biopsy from the right lung B² demonstrated lymphocytic infiltration and fibrous thickening of the septum. No neutrophilic infiltration, granuloma, or giant cells representing phagocytosis of foreign bodies were found (Fig. 5).

After hospitalization, MTX therapy was discontinued, and the ground-glass opacity in the upper lobe of the right lung gradually disappeared without corticosteroids or any other antibiotics. The contrast medium-enhanced CT on the 26th day showed only a slight scar in the right lung's upper lobe and no disruption of blood flow (Fig. 6).

She was discharged from the hospital in good health and with stable respiratory status on the 28th day.

3. Discussion

MTX-ILI is a widely known adverse event like other drug-ILIs, MTX-ILI typically manifests radiologically with shadows in both lungs [1]. One case of unilateral MTX-ILI was reported previously [2], in which a physician evaluation with bronchoscopy was performed, but the only laboratory tests performed were complete blood cell counts and urinalysis. No diagnostic method is specific for drug-ILI [1]. Thus, it is important to rule out other diseases, discontinue the suspect drug in hopes of improving imaging findings, and worsen the condition by readministering the drug. In MTX-ILI, the appearance of new shadows on imaging studies, the absence of causal organisms in blood and sputum, and the pathological findings are especially important [3]. DLST is an available adjunct diagnostic test, but DLST for MTX has low specificity and yields many false-positive results [4]. In patients with MTX-ILI, BALF demonstrates increases in lymphocyte levels and a high CD4/CD8 ratio. Because the CD4/CD8 ratio is low in patients with other drug-ILIs, such as interstitial lung disease, a high CD4/CD8 ratio is of great diagnostic significance in MTX-ILI [5]. The main pathological findings of MTX-ILI are interstitial infiltration by lymphocytes, histiocytes, and eosinophils, with or without granulomas [6].

No findings were suggestive of atypical pneumonia, antimicrobial infection, fungal infection, pneumocystis pneumonia, or cytomegalovirus infection in our patient. Although the results of DLST were positive for MTX, these did not confirm MTX-ILI yet. The patient's BALF exhibited characteristic increases in lymphocyte levels and a high CD4/CD8 ratio, and transbronchial lung biopsy revealed lymphocytic infiltration. Discontinuation of MTX seems to have resulted in improvement in the ground-glass opacity of the right lung. In our patient, MTX was not readministered. MTX-ILI is thought to be a hypersensitivity reaction, and relapse does not often occur with readministration [7].

Although unilateral drug-ILI has often been reported, many affected patients have, in fact, exhibited lesions in both lungs [1]. Only 12 cases of actual unilateral drug-ILI have been previously reported (Table 2) [2,8–18]; of these, one case involved MTX [2], two involved amiodarone [8,9], and one each involved balsalazide [10] and mesalamine [19] (both of which are 5-aminosalicylic acid drugs). These medications are often reported to cause drug-ILI, and patients who take them may also be prone to unilateral drug-ILI. In one case of unilateral nivolumab-ILI, aspiration of saliva or blood may have been the trigger [12]. In addition, three cases of unilateral drug-ILI were reported after surgery for lung cancer [13–15]. After surgery, immune cells are stimulated, and inflammatory cytokines are released. Goda et al., therefore, hypothesized that the residual postoperative lung is more prone to drug-ILI, in view of the inflammatory cytokine release [14].

In our patient, MTX-ILI developed 2 years after MTX treatment and had an acute presentation after aspiration of foreign bodies. Previous reports have shown that aspiration and surgery, which increase inflammatory cytokines, can lead to unilateral drug-ILI. In addition, foreign bodies in the airways, especially organic foreign bodies, can increase the expression of inflammatory cytokines [19, 20]. Therefore, we hypothesized that unilateral MTX-ILI was secondary to aspiration of the airway foreign bodies, which increased the expression of inflammatory cytokines. We found no previous reports of concomitant foreign bodies in the airways and drug-ILI. Our patient might represent the first case in which foreign bodies in the airways, especially organic ones, have caused unilateral drug-ILI. Further investigations are needed to elucidate the relationship between unilateral drug-ILI and foreign bodies in the airways.

4. Conclusion

MTX-ILI does occur unilaterally. Foreign bodies in the airways might also trigger unilateral MTX-ILI.

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Declarations of competing interest

The authors declare that they have no competing interests.

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