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Abstract

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KEYWORDS: drug-induced interstitial lung disease, trimethoprim/sulfamethoxazole, clinical characteristic, radiographic findings

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Original Article

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We studied clinical and radiographic features of interstitial lung disease (ILD) during trimethoprim/sulfamethoxazole (TMP/SMX) administration. Ten patients who had received prednisolone treatment for underlying diffuse pulmonary disease showed various ILDs after introduction of TMP/SMX. The radiographic features of the ILDs were not consistent with infectious disease or exacerbation of the underlying disease, and these diagnoses were excluded radiographically and on clinical grounds during the differential diagnosis of the ILDs. These ILDs emerged relatively early after introduction of TMP/SMX, which is consistent with the former case report of drug-induced ILD (DI-ILD) caused by TMP/SMX. Therefore DI-ILDs caused by TMP/SMX were suspected in these cases. In most of these cases, the ILDs were clinically mild and disappeared immediately although administration of TMP/SMX was continued.

Key words: drug-induced interstitial lung disease, trimethoprim/sulfamethoxazole, clinical characteristic, radiographic findings

Interstitial lung diseases (ILDs) represent a very large group of more than 200 different entities, many of which are rare diseases [1]. Recently, conventional drugs have emerged as relatively common and significant inducers of diffuse ILD, as well as of pleural and pulmonary vascular disease [2]. These kind of drug reactions, in other words, drug-induced interstitial lung disease (DI-ILD), constitute one of the major diagnostic challenges in pulmonary medicine. This is especially the case immunocompromised hosts, in whom DI-ILD is estimated to account for 5% to 30% of all pulmonary complications. Such reactions must be distinguished from the opportunistic infections and disease recurrence they mimic both clinically and radiographically. In this setting, the identification of a drug-related etiology of a patient's disease may be difficult because of a lack of specific clinical, functional, or radiographic findings [3]. The widely accepted criteria of DI-ILD are as follows. First, there should be a history of drug exposure. Secondly, the clinical, imaging, and pathologic pattern of drug involvement should conform to earlier observations with the drug. Thirdly, etiology of lung disease other than drugs should be ruled out. Fourthly, improvement should follow discontinuation of the suspected drug. And finally, symptoms should recur on rechal-

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lenge [4]. Trimethoprim, a trimethoxybenzylpyrimidine, inhibits bacterial dihydrofolic acid reductase about 50,000 times more efficiently than the same enzyme of mammalian cells. When given together with sulfonamides, trimethoprim produces sequential blocking in this metabolic sequence, resulting in marked enhancement of the activity of both drugs. Infections with *Pneumocystis jiroveci* and some other pathogens can be treated orally with high doses of the combination (dosed on the basis of the trimethoprim component at 15–20 mg/kg) or can be prevented in immunosuppressed patients by one double-strength tablet daily or 3 times weekly [5]. According to previous reports, TMP/SMX would cause ILD, pulmonary infiltration with eosinophilia, pulmonary edema, or noncardiogenic pulmonary edema [6–10], but there have been few case reports of DI-ILD caused by TMP/SMX.

Here we report ten patients with a range of ILDs that were found incidentally by chest CT scans obtained during the course of observing the underlying disease.

Materials and Methods

We studied characteristics of the background, clinical course, and radiographic features of 10 patients who showed abnormal shadows after the administration of TMP/SMX during the treatment of the underlying diffuse pulmonary diseases. This study, conducted from 2005 to 2008 at the National Hospital Organization Sanyou Hospital, included 4 men and 6 women with a median age of 71 years (range: 60 to 84 years). Seven patients had interstitial pneumonia, 2 had pulmonary vasculitis, and one had dermatomyositis. Eight patients received TMP/SMX as prophylaxis, and 2 patients received it as treatment. Table 1 shows the dose and schedule of TMP/SMX. Clinical characteristics of the patients and the time course of the abnormal shadow of the lung were recorded. Radiographic characteristics were described based on the findings of CT scanning. We defined ILD as a pulmonary abnormality that can be detected by chest CT imaging, and that showed an infiltrative shadow in the pulmonary parenchyma. Chest CT with an Asteion CT scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) was performed to assess the effect of the treatment on the underlying disease. The images of the patients were acquired under the following conditions: collimation of 2 mm; field of view of 200 mm; slice intervals of 0.75 s; operation at 120 kV; 150 mA tube filament current; lung window adjustment; center and width of −600 and 1,600 HU, respectively; and image reconstruction with a 512×512 pixel matrix. A filter was applied to the high resolution algorithm for image reconstruction.

A diagnosis of DI-ILD caused by TMP/SMX was suspected when the following 3 criteria were met. (1) the pulmonary lesion was detected after the administration of TMP/SMX; (2) a diagnosis of infectious disease and pulmonary congestion was ruled out on clinical grounds; and (3) the suspected DI-ILD emerged or resolved, independently of the course of the underlying pulmonary disease.

Table 1 Characteristics of the cases*

Case	Age and sex	Underlying disease	Purpose of Administration	Dose of TMP/SMX	Frequency
1	70 y.o. female	Wegener's granulomatosis	Prophylaxis	80/400 mg	once a week
2	71 y.o. female	Interstitial pneumonia	Prophylaxis	80/400 mg	once a week
3	67 y.o. male	Interstitial pneumonia	Prophylaxis	80/400 mg	once a day
4	73 y.o. female	Interstitial pneumonia	Prophylaxis	80/400 mg	once a day
5	60 y.o. female	Dermatomyositis	Prophylaxis	80/400 mg	once a day
6	77 y.o. female	Interstitial pneumonia	Prophylaxis	80/400 mg	once a day
7	84 y.o. male	Acute lung injury	Prophylaxis	80/400 mg	once a day
8	71 y.o. male	Microscopic polyangiitis	Prophylaxis	80/400 mg	once a day
9	73 y.o. male	Interstitial pneumonia	Treatment	320/1,600 mg	twice a day
10	84 y.o. female	Interstitial pneumonia	Treatment	320/1,600 mg	twice a day

*TMP/SMX denotes trimethoprim/sulfamethoxazole.

Results

In addition to glucocorticoid, 2 and 5 of 10 patients received cyclophosphamide and cyclosporine, respectively, for treatment of the underlying disease. Nine of 10 patients took TMP/SMX more than 4 weeks after the initiation of reatment for the underlying disease. When TMP/SMX was introduced, no other medication was started at the same time. After the introduction of TMP/SMX, we found various ILDs on the CT scanning images of these cases. The time course and the radiologic characteristics of these ILDs are shown in Table 2 and 3, and in Figs. 1, 2 and 3.

None of the patients had any symptoms related to the ILDs, and thus we not identify the onset of the ILDs. The median time point of confirmation of the radiologic abnormality by CT scan was 11 days (range: 4 to 32 days) after the introduction of TMP/SMX. The lung lesion was detected within 14 days in 8 of 10 cases. After the detection of the pulmonary lesions, the administration of TMP/SMX was discontinued in 3 of 10 cases, and in the other 7 cases the administration was continued. In 9 of 10 cases, the pulmonary lesions disappeared at between 26 days and 90 days after introduction of TMP/SMX. In 5 of 8 cases for prophylaxis the pulmonary lesions disappeared within 56 days after introduction. One of 2 cases receiving TMP/SMX for the purpose of treatment was left with a scar (Table 2).

During the observation period, the course of the underlying diseases had no relation to the ILDs. Typical radiographic courses of the ILDs and the underlying diseases are shown in Figs. 4, 5 and 6. No abnormality related to the underlying lung disease was found by chest radiography in the 8 cases (cases

Table 2 Time course of the abnormality*

Case	Detection of abnormality after introduction of TMP/SMX	Course of the radiographic abnormality	Dose of PSL at the onset
1	19 days	Disappeared 48 days after introduction	40 mg
2	4 days	Disappeared 63 days after introduction	30 mg
3	11 days	Disappeared 33 days after introduction	30 mg
4	32 days	Disappeared 56 days after introduction	30 mg
5	12 days	Disappeared 39 days after introduction	30 mg
6	14 days	Disappeared 90 days after introduction	20 mg
7	14 days	Disappeared 26 days after introduction	30 mg
8	8 days	Disappeared 30 days fater introduction	60 mg
9	5 days	Disappeared 60 days after introduction	10 mg
10	6 days	Scarring 50 days after introduction	10 mg

*PSL denotes prednisolone.

Table 3 Features of the abnormal radiologic findings

Case	Distribution	Radiographic abnomality
1	Outer zone of left S3	Equivocal patchy area of ground glass opacity with air-bronchiologram.
2	Middle zone of left S1 + 2	Small area of ground glass opacity delineated by airway and vessel.
3	Middle zone of right S1, 2, 3	Equivocal patchy area of ground glass opacity
4	Middle and outer zone of right S2, S3	Patchy area of infiltration. Weak lesions have obscure border and strong ones have clear border.
5	Middle zone of left S1 + 2	Irregular-shaped opacification around bronchovascular bundle
6	Outer zone of right S4	Equivocal patchy area of ground glass opacity with air-bronchiologram
7	Middle and outer zone of left S3	Equivocal patchy area of infiltration
8	Outer zone of bilateral S9, S10	Well-demarcated band and nodular shadow
9	Middle and outer zone of bilateral S2	Equivocal infiltration
10	Middle and outer zone of bilateral S1, 2	Widespread infiltration, partially with clear border and in other part with equivocal border.

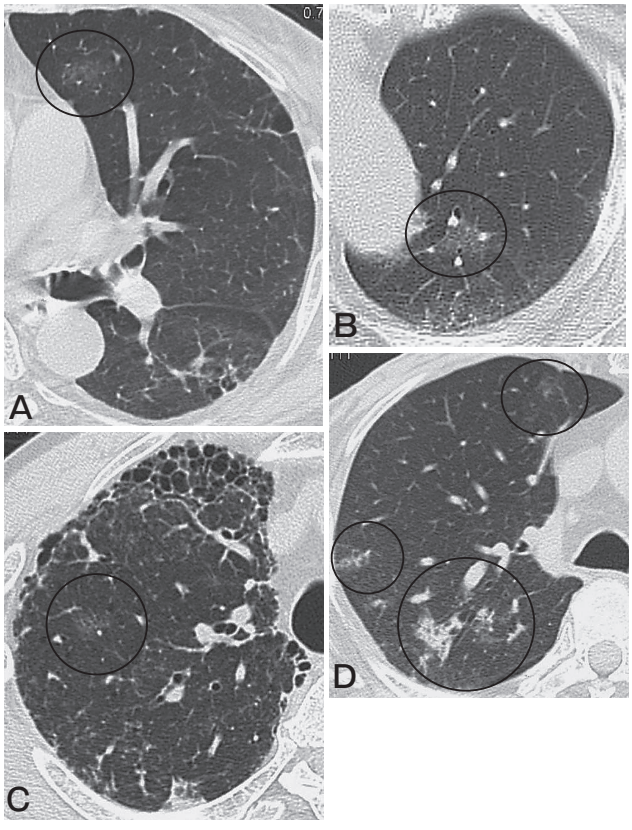

Fig. 1 Panel A shows patchy shadows in the outer zone of left S3, as observed in case 1. Panel B shows a small increase in density in the middle zone of left S1 + 2, as observed in case 2. Panel C shows infiltration in the middle zone of right S1, S2, S3, as observed in case 3. Panel D shows patchy areas of infiltration in the middle and outer zone of right S2, S3, as observed in case 4. The weak lesions had obscure borders and the strong ones had clear border. Ovals indicate abnormal shadows that appeared after the administration of TMP/SMX.

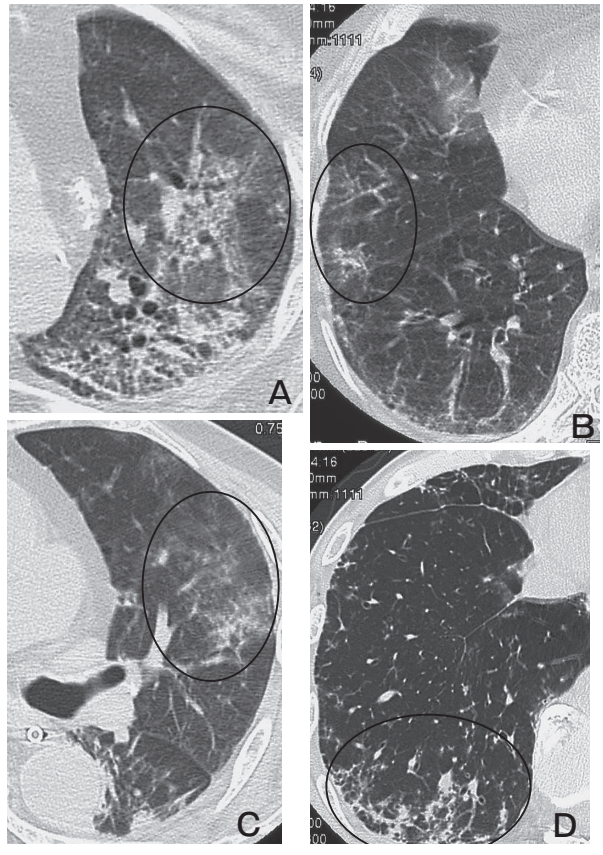

Fig. 2 Panel A shows irregular-shaped infiltration in the middle zone of left S1 + 2, as observed in case 5. Panel B shows patchy infiltration in the outer zone of right S5, as observed in case 6. Panel C shows patchy area of infiltration in the left S3, as observed in case 7. Panel D shows the well-demarcated band and nodular shadows in the outer zone of left S9, S10, as observed in case 8. This case had bilateral pulmonary infiltration. Ovals indicate abnormal shadows that appeared after the administration of TMP/SMX.

1 to 7, and 9) because pulmonary lesions were not severe. In analyzing the radiologic image patterns of the CT scan obtained from all 10 cases, 7 cases showed pulmonary lesions in the ipsilateral lungs, and 3 cases showed pulmonary lesions in both lungs. In the 7 cases patients for whom the lesions were limited to the ipsilateral lungs, the lesions were localized to the upper lobes in 6 cases, and to the middle lobe in one. Bilateral lesions were localized to the upper lobes in 2 cases, and to the lower lobe in one. To classify the pulmonary lesions according to the lung zones, in 3 cases they were distributed to the middle zone, in 4 cases they were spread from the middle to outer zones, and in the other 3 cases they were found in the outer zone (Table 3, Figs. 1, 2 and 3).

Concerning the relation to the pulmonary secondary lobule, we could not discern any relation between these pulmonary lesions and secondary lobule, because the borders of the lesions were often obscure, or the lesions were often localized in the middle zone of the lung, where it was difficult to identify the secondary pulmonary lobule.

In regard to the relation between the amount of TMP/SMX administered and the severity of the pulmonary lesions, the patient given the lowest dosage had the weakest radiologic abnormality (case 1), and the patient given the highest dosage had the strongest radiologic findings.

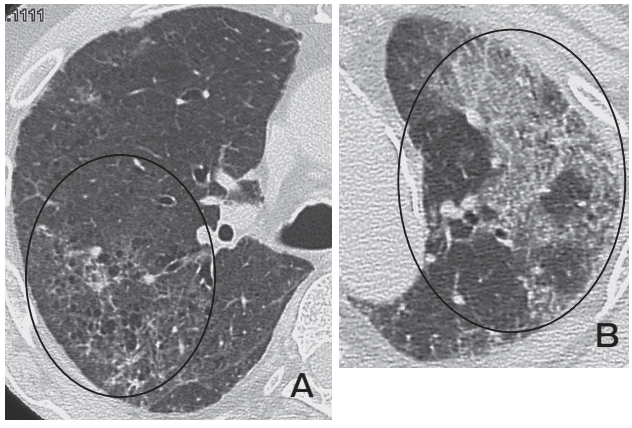

Fig. 3 Panel A shows infiltration in the middle and the outer zone of right S2, as observed in case 9. Panel B shows widespread infiltration in the middle and the outer zone of left S3, as observed in case 10. Cases 9 and 10 both showed bilateral pulmonary infiltration. Ovals indicate abnormal shadows that appeared after the administration of TMP/SMX.

Discussion

There have been few case reports on ILDs during the administration of TMP/SMX. In this article, we studied clinical and radiographic features of pulmonary lesions during TMP/SMX administration, while the patients were receiving treatment for underlying diffuse lung disease. In these patients, various ILDs were found after the introduction of TMP/SMX, which were not present at the beginning of the treatment for the underlying disease.

Because none of these cases had any clinical symptoms associated with drug-induced pulmonary injury, we could not observe the onset of the ILDs precisely. But the fact that pulmonary abnormalies were detected on the CT scan within 14 days after introduction of TMP/SMX in 8 of 10 cases indicates that these ILDs tended to occur relatively earlier, which is consistent with the former report of DI-ILD caused by TMP/SMX [6].

As to the radiographic features of the ILDs observed in this study, these ILDs are characterized as patchy shadows distributed from the middle to outer zones, mainly in the upper lungs. The secondary pulmonary lobule as defined by Miller refers to the smallest unit of lung structure marginated by connective tissue septa [11]. On CT scanning, it is possible to some extent to assume the histopathologic pattern

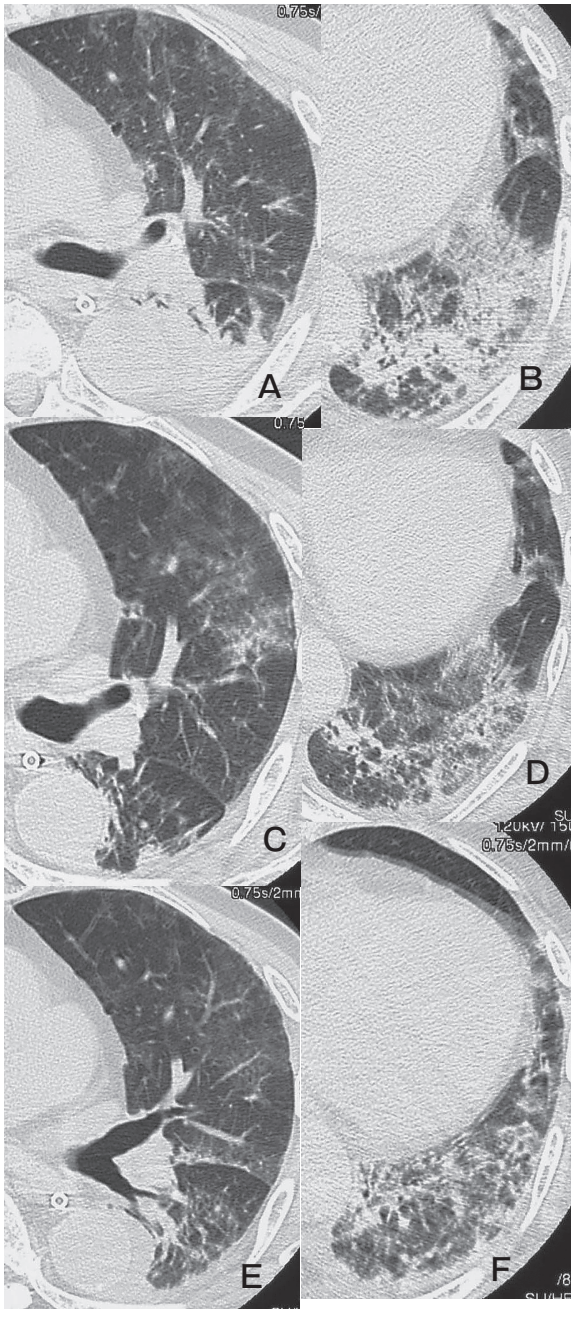

Fig. 4 Panels A and B show the HRCT findings in case 7 on the day of TMP/SMX introduction, panels C and D show the HRCT findings at 14 days after TMP/SMX introduction, and panels E and F show the findings at 40 days. Panels A and B show abnormal shadows of the underlying acute lung injury. Panels C and D show the emergence of irregular infiltration in the left upper lobe, and the improvement of consolidation in the left lower lobe. In panels E and F, the previously emerged infiltration in the left upper lobe has almost disappeared, while the diffuse infiltration in the left lower lobe and ground glass opacity seen in the dorsal part of the left upper lobe have worsened.

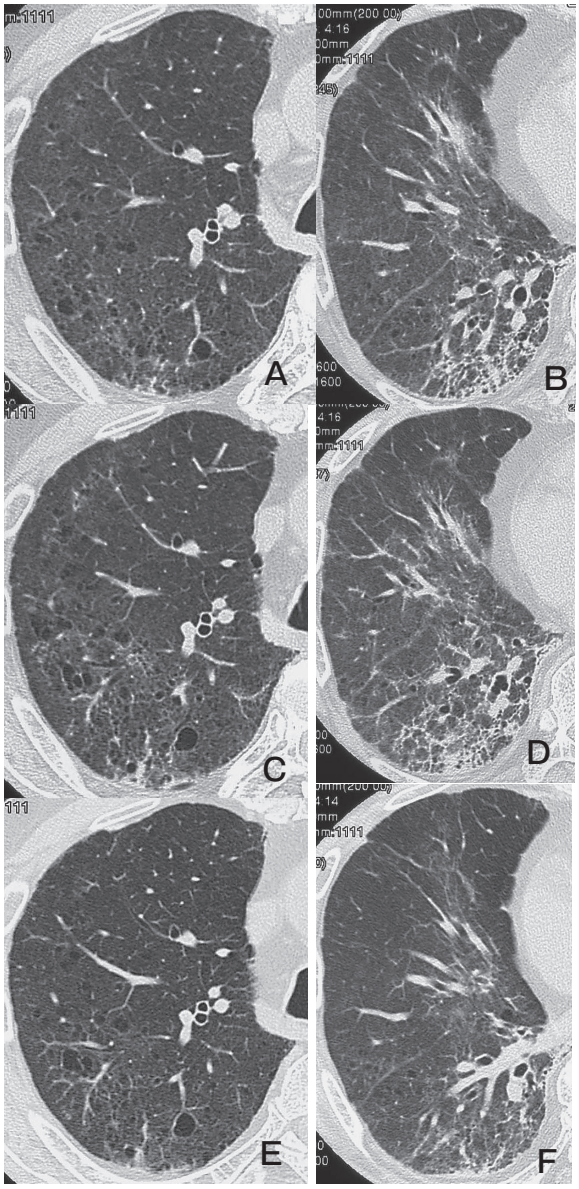

Fig. 5 Panels A and B show the HRCT findings in case 9 one day before TMP/SMX introduction, panels C and D show the HRCT findings 5 days after TMP/SMX introduction, and panels E and F show the findings 60 days after introduction. The diffuse infiltration in the periphery of the right upper lobe in panel A and the reticular opacity in the right lower lobe in panel B represent the underlying interstitial pneumonia. This patient received TMP/SMX for 3 days and then the medication was discontinued because of nausea. Irregular infiltration in the middle and the outer zone of right S2 has emerged in panel C, while the underlying reticular opacity in the right lower lobe remains stable in panel D. The previously emerged infiltration in the right upper lobe has disappeared in panel E, and the reticular shadow in the right lower lobe is improved in panel F.

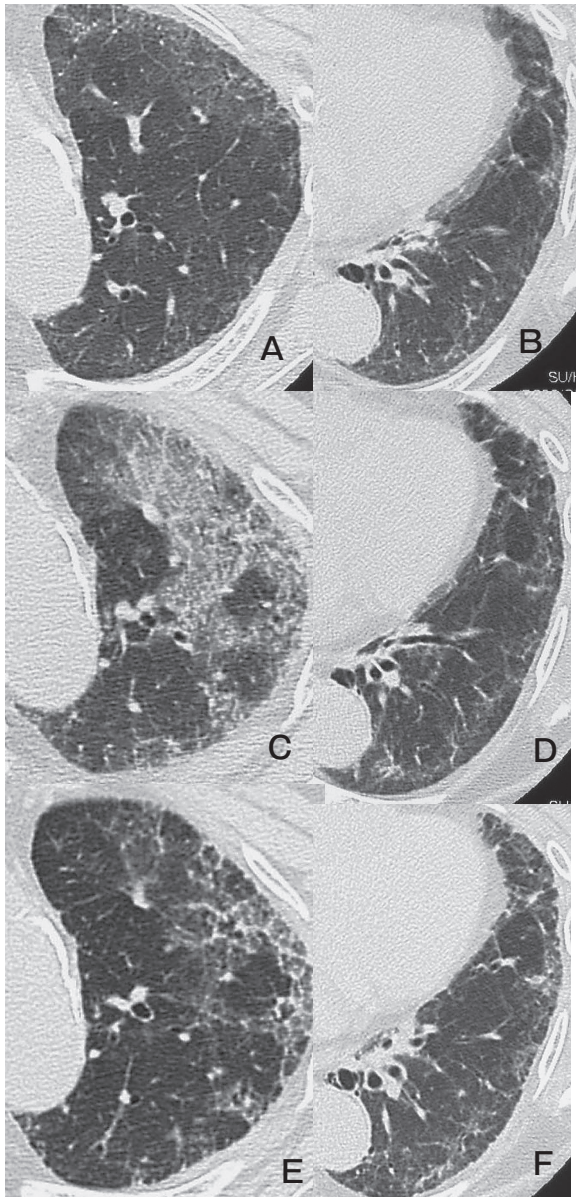

Fig. 6 Panels A and B show the HRCT findings in case 10 one day before TMP/SMX introduction, panels C and D show the HRCT findings 6 days after TMP/SMX introduction, and panels E and F show the findings 50 days after introduction. The diffuse infiltration in the periphery of the left upper lobe in panel A and small nodular shadows in the left lower lobe in panel B represent the underlying interstitial pneumonia. The irregular infiltration in the middle and the outer zone of left S1 + 2 have emerged in panel C, while the underlying reticulonodular shadow in the left lower lobe remained stable in panel D. This patient received TMP/SMX for 8 days and then the medication was discontinued because of suspected drug-induced interstitial lung disease. Panel E shows that the previously emerged infiltration in the left upper lobe resolved but left scarring, and panel F shows the slight worsening of the reticular opacity in the left lower lobe.

of the lesion from its radiologic imaging pattern in relation to the anatomy of the pulmonary secondary lobule. And it is easier to recognize a secondary lobule that is on the periphery of the lung, and more difficult for that in middle zone or inner zone of the lung. Most of the present cases that showed abnormal findings had lesions with obscure border, or lesions in the middle zone where pulmonary secondary lobules are difficult to identify, and thus we could not descern the relation between the ILDs and secondary lobules in these cases, and consequently it was not possible to assume the histopathologic pattern of these lesions.

Radiographically, these ILDs were so characterless that neither infectious disease nor exacerbation of the underlying disease seemed an appropriate diagnosis. Because the diagnoses of infectious disease and exacerbation of the underlying disease were excluded on clinical grounds and radiographically, the alternative diagnosis of DI-ILDs caused by TMP/SMX was suspected in these cases.

In 7 of 8 patients (cases 1 to 7) to whom prophylactic administration was given, the chest abnormal shadow was relieved despite the continuous administration of TMP/SMX. These were considered cases of "transient pulmonary infiltration", which is recognized as a chest radiographic abnormality without significant clinical symptoms and occurring for only a short period of time. Seven of the 8 patients who received a prophylactic dose of TMP/SMX showed ILDs in the ipsilateral lungs, and in 6 of these cases the ILDs appeared in the upper lobe. From this observation, a patient receiving a prophylactic dose of TMP/SMX will tend to show a trifling shadow in the upper lobe. Both of the patients who were treated with a therapeutic dose of TMP/SMX showed abnormalities in the bilateral upper lobe. Comparing this finding with that of the abnormalities found in the patients taking a prophylactic dose, there would seem to be some relation between the dosage of TMP/SMX and the intensity of the pulmonary lesion.

In conclusion, we studied a range of ILDs found by chest CT imaging after TMP/SMX administration for patients with underlying diffuse pulmonary diseases. Considering the mild clinical course of these cases, and the absence of CT findings indicative of infectious diseases or exacerbation of the underlying diseases, we suspected that these lesions were DI-ILDs caused by TMP/SMX.

References

1. Demedts M, Wells AU, Anto JM, Costabel U, Hubbard R, Cullinan P, Slabbynck H, Rizzzato G, Poletti V, Verbeken EK, Thomeer MJ, Kokkarinen J, Dalphin JC and Taylor AN: Interstitial lung diseases: an epidemiological overview. Eur Respir J Suppl (2001) 18: 2s–16s.
2. Camus Ph, Foucher P, Bonniaud Ph and Ask K: Drug-induced infiltrative lung disease. Eur Respir J Suppl (2001) 18: 93s–100s.
3. Fraser RS, Neil C, Nestor LM and Pare PD: Fraser and Paré's Diagnosis of Diseases of the CHEST, 4th Ed, WB Saunders, Philadelphia (1999) pp 2537–2540.
4. Camus Ph: Drug Induced Infiltrative Lung Diseases. Shwarz King Interstitial Lung Disease, 4th Ed, BC Decker, London (2003) pp 485–534.
5. Henry FC: Sulfonamides, Trimethoprim, & Quinolones. Basic & Clinical Pharmacology, 9th Ed, McGraw Hill, New York (2004) pp 773–777.
6. Hashizume T, Numata H and Matsushita K: Drug-induced Pneumonitis Caused by Sulfamethoxazole -trimethoprim. Nihon Kokyuki Gakkai Zasshi (2001) 39: 664–667 (in Japanese).
7. Cass RM: Adult respiratory distress syndrome and trimethoprim-sulfamethoxazole. Ann Intern Med (1987) 106: 331.
8. Holdcroft CJ and Ellison RT: Trimethoprim-sulfamethoxazole reaction simulating *Pneumocystis carinii* pneumonia. AIDS (1991) 5: 1029.
9. Oshitani N, Matsumoto T, Moriyama Y, Kudoh S, Hirata K and Kuroki T: Drug-induced pneumonitis caused by sulfamethoxazole, trimethoprim during treatment of *Pneumocystis carinii* pneumonia in a patient with ulcerative colitis. J Gastroenterol (1998) 33: 578–581.
10. Yamagishi T, Yoshida S, Hukutake K, Utsumi K and Ichinose Y: Sulfamethoxazole-trimethoprim induced pneumonitis in a patient with hemophilia B who was infected with the human immunodeficiency virus. Nihon Kyobu Shikkan Gakkai Zasshi (1996) 34: 822–888 (in Japanese).
11. Richard W, Nestor LM and David PM: High-Resolution CT of the Lung. 3rd Ed, Lippincott Williams & Wilkins, Philadelphia (2001) pp 51–59.