Pneumonitis Induced by Rifampicin: A Case Report and Literature Review


Abstract

An 84-year-old woman being treated for miliary tuberculosis (TB) with rifampicin (RFP), isoniazid (INH), ethambutol (EB) and corticosteroids suffered from a persistent fever for five months. While tapering the dose of prednisolone, chest computed tomography (CT) revealed diffuse ground glass opacities (GGO) and bronchoalveolar lavage fluid (BALF) showed an increase in lymphocytes. After the anti-TB drugs were discontinued and the dose of the corticosteroids was increased, the CT findings and fever improved considerably. However, readministration of RFP provoked an inflammatory reaction, leading to a diagnosis of RFP-induced pneumonitis. This condition is very rare. This is the first report of RFP-induced pneumonitis occurring during adjunct steroid therapy.

Key words: rifampicin, miliary tuberculosis, drug-induced pneumonitis, corticosteroid, bronchoalveolar lavage fluid

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Introduction

The use of combination therapy is fundamental to controlling miliary tuberculosis (TB). Since it was first introduced in 1967, rifampicin (RFP) has been used widely as a key drug for treating both TB and nontuberculous mycobacterial infections.

Generally, combination therapy is very effective against TB, with the exception of multidrug-resistant *Tubercle bacilli*. Although anti-TB therapy is effective, patients sometimes suffer persistent spikes in fever, weight loss and anorexia. In such cases, physicians reluctantly use corticosteroids as adjunct therapy to improve the patient’s clinical condition.

Adverse events induced by anti-TB drugs are another serious problem that can occur during combination TB therapy. The most common adverse events associated with RFP are hepatotoxicity, nephrotoxicity, skin rashes and drug-induced fever (1). Pneumonitis induced by RFP may also occur, however, despite universal use of this drug, the condition is very rare. In particular, there are no reported cases of pneumonitis induced by RFP in which the patient had received corticosteroids as adjunct therapy. We herein report a case of RFP-induced pneumonitis in a patient with miliary TB who was treated with adjunct corticosteroid therapy.

Case Report

An 84-year-old Japanese woman was taken to the hospital by ambulance due to melena. On arrival, her body temperature was 37.3°C, her blood pressure was 178/74 mmHg, her SpO₂ was 82% and her pulse was 77 beats/min. She had suffered from a fever that had persisted for six weeks and had been prescribed cefmetazole for a few days due to suspicion of a urinary tract infection. She had also been prescribed famotidine for several years. She had never smoked. She had no history of any allergies. On admission, her body weight was 43.6 kg and her height was 151.0 cm.

A blood count test showed a decreased hemoglobin level...
of 7.4 mg/dL and a normal white blood cell (WBC) count of 3,900/μL. The laboratory data showed an elevated C-reactive protein (CRP) level of 4.21 mg/dL. Colonoscopy revealed the presence of an ulcer in the lower rectum with an exposed interior vessel that was ligated with a single elastic band. Repeat colonoscopy showed that the lesion had healed with a scar and the bleeding had stopped.

To determine the cause of the fever, screening examinations were carried out, including thoracoabdominal computed tomography (CT). Chest X-ray and chest CT showed multiple diffuse nodules sized between 2-3 mm in both lungs (Fig. 1A, B). An abdominal CT scan showed enlargement of the para-aortic and iliac lymph nodes (size 10 to 27 mm). A loop-mediated isothermal amplification (LAMP) as-

Figure 1. Chest CT images. (A and B) Before initiation of anti-TB drugs. Diffuse multiple nodules are seen in both lungs. (C and D) After 12 weeks of anti-TB therapy when pneumonitis occurred. GGO appeared in both lung fields. (E and F) After readministration of RFP. The white arrows show newly developed GGO. (G and H) After steroid therapy was stopped and the patient had been discharged. TB: tuberculosis, GGO: ground glass opacities, RFP: rifampicin
say of sputum was positive, leading to the patient being diagnosed with miliary TB. (Later, cultivation of sputum detected *Mycobacterium tuberculosis* with no anti-TB drug resistance). The patient was transferred to a tubercular hospital and started on combination therapy that included isoniazid (INH, 200 mg), RFP (300 mg) and ethambutol (EB, 500 mg).

Even after initiation of these anti-TB drugs, the patient continued to suffer from a fever above 38°C (Fig. 2). Treatment with prednisolone (PSL) at dose of 20 mg was started to reduce the fever and increase the patient’s appetite. As shown in Fig. 2, the frequency of temperature spikes decreased; therefore, the steroid dose was gradually reduced to 5 mg of PSL every second day. EB was discontinued after 12 weeks of TB therapy, and the patient was subsequently discharged.

After discharge, the patient continued to suffer from a fever up to 38°C. When she returned to our hospital for follow-up therapy as an outpatient, her SpO2 was 91%, her body temperature was 37.4°C, her blood pressure was 124/58 mmHg and her pulse was 96 beats/min. Her WBC count was 5,900/μL with 81.4% neutrophils, 0.8% eosinophils, 4.7% monocytes and 12.8% lymphocytes. The laboratory data showed an elevated CRP level of 15.84 mg/dL and a KL-6 level of 2,341 U/mL. A CT scan showed newly developed ground glass opacities (GGO) in both lung fields, while the small nodules seen before the initiation of anti-TB therapy had disappeared (Fig. 1C, D). A serum biochemistry analysis and sputum culture suggested no signs of infection. A bronchoscopic examination demonstrated an increased percentage of lymphocytes (58%) in the bronchoalveolar lavage fluid (BALF). In contrast, the percentages of neutrophils (9%), eosinophils (1%) and macrophages (30%) had not increased. The CD4/CD8 ratio was 1.26. The results of drug-induced lymphocyte-stimulating tests (DLST) using RFP, INH and EB were all negative.

On the basis of these findings, we strongly suspected a diagnosis of pneumonitis induced by anti-TB drugs. All anti-TB drugs were therefore discontinued, and 40 mg/day of PSL was started immediately. The steroid therapy caused a dramatic improvement in the fever, and the GGO disappeared. The dose of PSL was then gradually reduced to 10 mg/day.

On the 24th day of the second hospitalization, 25 mg of RFP was readministered as desensitization therapy. This resulted in the reappearance of a fever above 37°C, and the levels of CRP and LDH increased slightly from 0.07 to 1.23 mg/dL and 171 to 224 IU/L, respectively. A CT scan also revealed a new GGO in the left upper lobe (Fig. 1E). A relapse in pneumonitis caused by RFP was strongly suspected; therefore, the drug was discontinued, and 25 mg of INH was started as desensitization therapy combined with 500 mg/day of levofloxacin (LVFX) and 750 mg of streptomycin (SM) twice a week. The dose of steroids was gradually reduced and the dose of INH was gradually increased. No signs of pneumonitis were apparent on CT (Fig. 1G, H) or in the results of physical and laboratory examinations, and the patient was discharged 28 days after the readministration of INH without PSL. These agents were administered for an additional three months without any signs of recurrence of pneumonitis.

**Discussion**

Fever is a common symptom in patients undergoing TB therapy. Distinguishing the cause of fever from the initial aggravation of TB, persistent symptoms of TB and adverse effects of anti-TB drugs is difficult, although it is important for subsequent treatment.

Combination TB therapy is relatively effective for miliary TB, although in some cases, symptoms such as fever may persist despite CT and sputum bacillary count examinations showing improvement. Evidence for the use of steroids in these cases has not been clearly demonstrated, and only a
small number of studies have shown beneficial responses in patients with pulmonary TB (2, 3). In particular, no study has specifically evaluated the role of adjunct steroid treatment in patients with miliary TB (4). In the current case, steroids were used reluctantly, with the spikes in fever improving slightly following their introduction (Fig. 2). X-ray performed in April under the administration of steroid therapy showed no signs of pneumonitis; however, when the patient was readmitted in May, a new GGO had appeared. Although we were not able to determine the exact timing of onset, the pneumonitis had developed between 10 to 12 weeks during tapering of the PSL dose following the initiation of the anti-TB drugs.

To our knowledge, there are five reports of patients with pneumonitis induced by RFP (Table) (5-9). All cases, except for the case not described, involved patients with pulmonary TB who were treated with RFP, INH and EB. All previous patients were men and had fever as a common symptom. The onset of RFP-induced pneumonitis ranged from three days to 13 weeks after the initiation of treatment and showed a bimodal pattern with early and late onset. Our patient showed late onset, with steroids possibly contributing to the development of pneumonitis. In addition, steroids can mask elevations in fever, making it difficult to diagnose drug-induced pneumonitis. Conversely, it is also possible that reducing the dose of PSL provoked RFP-induced pneumonitis.

On the other hand, the findings of BALF cell examinations showed a marked increase in the number of lymphocytes. Pulmonary TB itself sometimes causes increases in lymphocytes, with the number tending to correlate with the progression of the disease (10). The mean percentage of lymphocytes in patients with pulmonary TB has been reported to range between 11% and 20%, whereas in our case, it was 50%. We concluded that this was a significant increase (10).

The findings of DLST, a method for testing drug hypersensitivity, were negative in this case. These results might be caused by cytotoxic mechanisms or by a false negative reaction due to steroid-induced immune suppression. However, the validity of DLST for testing anti-TB drugs remains controversial, and only two previously reported patients with RFP-induced pneumonitis were positive for DLST (6, 8). In fact, the sensitivity of DLST for RFP has been reported to be only 13.6% (11), while another report concluded that DLST is not useful for diagnosing drug-induced pneumonitis (12).

The key drugs used in combination therapy for TB are INH and RFP, and physicians try to administer them as much as possible. In 1997, the Japanese Society for Tuberculosis (JST) proposed the use of desensitization therapy for these drugs, and evidence of its efficacy has been reported (13, 14). Subsequently, the JST also stated in their guidelines that readministration of anti-TB drugs should be limited to patients with adverse events such as liver injury and that desensitization is forbidden in patients with drug-induced pneumonitis (15). However, taking into account the therapeutic value of these drugs, their continued use should be considered on a case-by-case basis. In fact, there is one report of a patient who was successfully desensitized to INH-induced pneumonitis (16). As pneumonitis induced by RFP is very rare compared to that induced by INH or EB, we initially administered 25 mg of RFP, as described in the proposed JST guidelines. The presence of a low-grade fever, an increased LDH level and the appearance of GGO led us to unintentionally identify RFP as the responsible agent and therefore discontinue RFP desensitization.

In this case, pneumonitis occurred under low-dose PSL therapy. One report showed that even with low-dose PSL, T lymphocytes are slightly reduced in the circulation, which may indirectly influence onset mechanisms of T-cell mediated drug-induced pneumonitis (17). Therefore, PSL might have influenced the onset of RFP-induced pneumonitis somewhat in this case. The mechanisms underlying RFP-induced pneumonitis are currently undefined; however, the increased number of lymphocytes in BALF, the relapse induced by the readministration of RFP and the prompt clinical improvement achieved by discontinuing RFP and initiat-

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**Table. Clinical Features of Reported Cases of RFP-induced Pneumonitis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Primary disease</th>
<th>Initial treatment</th>
<th>Onset</th>
<th>Symptoms</th>
<th>DLST</th>
<th>% lymph BALF</th>
<th>CD4/CD8</th>
<th>Pneumonitis treatment</th>
<th>Anti-TB after pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umeki</td>
<td>79</td>
<td>M</td>
<td>pTB</td>
<td>RFP,INH,EB</td>
<td>13 wk</td>
<td>fever dyspnea (-)</td>
<td>NW</td>
<td>NW</td>
<td></td>
<td>PSL</td>
<td>INH,EB</td>
</tr>
<tr>
<td>Kunichika</td>
<td>81</td>
<td>M</td>
<td>pTB</td>
<td>RFP,INH,EB</td>
<td>9 d</td>
<td>fever dyspnea (+)</td>
<td>82.9%</td>
<td>10.5</td>
<td></td>
<td>mPSL→PSL cessation of anti-Tb drugs</td>
<td>INH,EB, SM</td>
</tr>
<tr>
<td>Nishio</td>
<td>86</td>
<td>M</td>
<td>pTB</td>
<td>RFP,INH,EB</td>
<td>3 wk</td>
<td>fever rash (-)</td>
<td>NW</td>
<td>NW</td>
<td></td>
<td>PSL</td>
<td>EB,SM, LVFX</td>
</tr>
<tr>
<td>Ashitani</td>
<td>83</td>
<td>M</td>
<td>pTB</td>
<td>RFP,INH,EB</td>
<td>12 wk</td>
<td>fever dyspnea (+)</td>
<td>14%</td>
<td>2.04</td>
<td></td>
<td>PSL</td>
<td>NW</td>
</tr>
<tr>
<td>Akira</td>
<td>39</td>
<td>M</td>
<td>NW</td>
<td>NW</td>
<td>3 d</td>
<td>fever chest pain</td>
<td>NW</td>
<td>NW</td>
<td></td>
<td>NW</td>
<td>NW</td>
</tr>
<tr>
<td>Author</td>
<td>85</td>
<td>F</td>
<td>mTB</td>
<td>RFP,INH,EB</td>
<td>10-12 wk (?)</td>
<td>fever (-)</td>
<td>58%</td>
<td>1.26</td>
<td></td>
<td>PSL</td>
<td>INH,SM, LVFX</td>
</tr>
</tbody>
</table>

ing steroids suggest that the progression of this case was based on an allergic effect. Further studies are needed to elucidate the precise mechanisms.

We experienced a case of RFP-induced pneumonitis, which is very rare. Notably, the patient was receiving adjunct steroid therapy. Adjunct steroids are not a defined therapy, although they may be effective for relieving intolerable symptoms caused by TB. However, steroid use can mask the adverse effects of anti-TB drugs, making it difficult for physicians to detect complications. The use of steroids must therefore be introduced very carefully, and if pneumonitis is suspected, BALF may be useful for diagnosing the condition.

The authors state that they have no Conflict of Interest (COI).

References


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