Mesalazine-induced Pleuropericarditis in a Patient with Crohn’s Disease

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Abstract

A 16-year-old boy was diagnosed with Crohn’s disease. Treatment with oral mesalazine was started at 3 g per day; however, he complained of high fever, a nonproductive cough, and left shoulder pain after 2 weeks. His chest radiography and chest computed tomography showed cardiomegaly and left pleural effusion, while an echocardiogram revealed pericardial effusion. Because no infection was detected by thoracentesis and the drug lymphocyte stimulation tests for mesalazine were positive, the patient was diagnosed with mesalazine-induced pleuropericarditis. After the cessation of mesalazine, the clinical symptoms and laboratory findings quickly improved.

Key words: mesalazine, pleuropericarditis, Crohn’s disease

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Introduction

Mesalazine plays a central role in the treatment of patients with inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC). Pleuropericarditis is reported both as a rare extraintestinal inflammatory manifestation of IBD and as an adverse side effect of mesalazine administration. Therefore, the differential diagnosis of pleuropericarditis is of importance for a patient with IBD who has started mesalazine treatment and developed unexplained fever and pleural effusion. The early diagnosis and treatment of pleuropericarditis is important because the condition is potentially life-threatening. Mesalazine-induced pleuropericarditis is very rare in CD patients. To the best of our knowledge, only two previous cases have been reported (1, 2). We herein report a case of mesalazine-induced pleuropericarditis in a 16-year-old boy with CD and discuss the current literature available regarding this condition.

Case Report

A 16-year-old boy visited our hospital because of bloody diarrhea and anal pain which had persisted for 2 months and was diagnosed with CD. Treatment with oral mesalazine at 3 g per day was started; however, a high fever of 39°C, a nonproductive cough, and left shoulder pain appeared after 19 days. His chest radiography and chest computed tomography (CT) showed cardiomegaly and left pleural effusion (Fig. 1a, c). Although the electrocardiogram was normal, the echocardiogram revealed pericardial effusion and global hypokinesia of the left ventricle, with the ejection fraction decreased to 55%. The laboratory data were within the normal ranges, with the exception of hemoglobin (12.5 g/dL), alanine aminotransferase (74 U/L), C-reactive protein (CRP) (13.7 mg/dL), and the erythrocyte sedimentation rate (95 mm). The tests for antinuclear antibodies and rheumatoid factor were negative. Fasting therapy was started because the exacerbation of his CD was suspected; however, the pleural effusion increased in size, and the high fever continued. The cultivation of the pleural effusion by thora-
Figure 1. Chest radiography showing the presence of left pleural effusion on day 23 of the mesalazine treatment (a) and its disappearance at 12 days after the cessation of the mesalazine treatment (b). Bilateral pleural effusion was observed on chest CT on day 23 of the mesalazine treatment (c).

Figure 2. Time course of the body temperature and the C-reactive protein (CRP) levels during the course of mesalazine treatment and subsequent to its cessation.

centesis showed no bacterial growth, but the drug lymphocyte stimulation tests (DLSTs) for mesalazine were positive. According to these findings, the patient was diagnosed with mesalazine-induced acute pleuropericarditis, and the administration of mesalazine was discontinued at day 33, which resulted in an immediate improvement of the clinical symptoms, the normalization of the CRP level after a week (Fig. 2), and the disappearance of left pleural effusion (Fig. 1b). The patient was treated with infliximab instead of mesalazine, and remission of CD was achieved with no recurrence of the pleuropericarditis.

Discussion

Acute pericarditis can develop in both UC and CD patients and has been reported to occur at a prevalence of 0.23% and 0.19% (3), respectively. Additionally, the drugs used to treat IBD, such as mesalazine, sulfasalazine, and azathioprine, can cause pleuropericarditis (4). Of the 18 cases of mesalazine-induced intrathoracic lesions (e.g., pleuropericarditis, pericarditis, myopericarditis, and pleuritis) that were identified by searching the PubMed database (Table) (1, 2, 5-19), only two cases experienced mesalazine-induced pericarditis with CD. The majority of the cases were patients with UC.

Distinguishing the etiology of acute pleuropericarditis is frequently difficult. Although acute pleuropericarditis has been reported to develop within 2-3 weeks of mesalazine initiation, the onset has also been reported to occur within a few days or many years after beginning treatment (2). The typical symptoms are dyspnea, fever, chest pain, and cough (4). While most of the cases were treated with steroids, rather than ceasing mesalazine treatment, the cessation of mesalazine results in symptom improvement after a few days to 2 weeks. However, a fatal case involving mesalazine-associated myocarditis has been reported (5). Although the mechanisms of mesalazine-induced pleuropericarditis remain unclear, immunoglobulin E-mediated allergic reaction, direct cardiac toxicity, humoral antibody response, and cell-mediated hypersensitivity have been suggested as possible mechanisms (6).

The diagnosis of mesalazine-induced pleuropericarditis is
often difficult because pleuropericarditis can be associated with other conditions. Hence, the exclusion of infectious diseases, such as viral or bacterial infection, is necessary. Other diseases that can be accompanied by pleuropericarditis (e.g., Wegener granulomatosis and bronchiolitis obliterans with organizing pneumonia) should also be ruled out. Although DLSTs for mesalazine have been reported to have a diagnostic significance in the confirmation of mesalazine-induced pleuropericarditis, as was true in the present case, some reports have documented that approximately one month is required for a patient to change from DLST negative to positive, and the highest reported positive rate of DLSTs is 42% (17). Furthermore, with the administration of generic medication, DLSTs for the generic medication compound are required. However, in the present case, because mesalazine was used, only the DLST for mesalazine was performed.

Given the common use of mesalazine in the treatment of CD, physicians should keep this potentially severe complication in mind. If CD patients treated with mesalazine com-

Table. Clinical Presentation, Therapy, and the Outcome of Mesalazine-induced Intrathoracic Lesions (e.g., pleuropericarditis, pericarditis, myopericarditis, and pleuritis).

<table>
<thead>
<tr>
<th>Reference</th>
<th>age, sex, IBD (UC or CD)</th>
<th>Medication (other than mesalazine)</th>
<th>Clinical presentation</th>
<th>occurrence (from initiation of mesalazine)</th>
<th>diagnosis</th>
<th>treatment (other than cessation of the drug)</th>
<th>prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>20, F, UC</td>
<td>-</td>
<td>chest pain, dizziness</td>
<td>13 days</td>
<td>myocarditis</td>
<td>isotropic support, artificial ventilation</td>
<td>died 22hour later</td>
</tr>
<tr>
<td>6</td>
<td>30, M, UC</td>
<td>-</td>
<td>fever, dyspnea, purpuric rash, ankle pain, chest pain</td>
<td>3 weeks</td>
<td>pericarditis, arthritis</td>
<td>hydrocortisone (20mg/day)</td>
<td>improved 2 days later</td>
</tr>
<tr>
<td>7</td>
<td>16, M, UC</td>
<td>prednisone</td>
<td>fever, dyspnea, chest pain</td>
<td>7 weeks</td>
<td>pleuropersicarditis</td>
<td>prednisone (20mg/day)</td>
<td>improved 8 days later</td>
</tr>
<tr>
<td>8</td>
<td>29, F, IBD</td>
<td>(the histology did not differentiate between the two type of IBD)</td>
<td>fever, dyspnea, cough, chest pain</td>
<td>7 weeks</td>
<td>pericarditis</td>
<td>methylprednisolone (1.25mg/day)</td>
<td>improved</td>
</tr>
<tr>
<td>2</td>
<td>53, M, CD</td>
<td>prednisone</td>
<td>fever, chest pain</td>
<td>8 years</td>
<td>pericarditis</td>
<td>prednisone</td>
<td>improved a few days later</td>
</tr>
<tr>
<td>9</td>
<td>17, M, UC</td>
<td>prednisolone</td>
<td>fever, chest pain, fatigue</td>
<td>2 weeks</td>
<td>pericarditis</td>
<td>prednisolone (60mg/day)</td>
<td>improved</td>
</tr>
<tr>
<td>10</td>
<td>41, F, colitis</td>
<td>prednisone</td>
<td>fever, chest pain, dyspnea</td>
<td>3 weeks</td>
<td>pericarditis</td>
<td>prednisolone (20mg/day)</td>
<td>improved</td>
</tr>
<tr>
<td>11</td>
<td>25, F, UC</td>
<td>-</td>
<td>fever, dyspnea, cough</td>
<td>2 weeks</td>
<td>pleuritis</td>
<td>methylprednisolone (40mg/day)</td>
<td>improved 1 day later</td>
</tr>
<tr>
<td>12</td>
<td>39, M, UC</td>
<td>methylprednisolone</td>
<td>fever, chest pain</td>
<td>2 days</td>
<td>myopericarditis</td>
<td>methylprednisolone</td>
<td>improved 36 hours laet</td>
</tr>
<tr>
<td>13</td>
<td>21, M, UC</td>
<td>budesonide</td>
<td>fever, dyspnea</td>
<td>10 days</td>
<td>myopericarditis</td>
<td>budesonide (9mg/day)</td>
<td>improved 1 week later</td>
</tr>
<tr>
<td>1</td>
<td>44, M, CD</td>
<td>-</td>
<td>chest pain</td>
<td>4 years</td>
<td>pericarditis</td>
<td>corticosteroid</td>
<td>improved a few days later</td>
</tr>
<tr>
<td>14</td>
<td>23, M, UC</td>
<td>-</td>
<td>fever, chest pain, dyspnea</td>
<td>3 days</td>
<td>pleuritis</td>
<td>none</td>
<td>improved 11 days later</td>
</tr>
<tr>
<td>15</td>
<td>54, M, UC</td>
<td>-</td>
<td>fever, chest pain, fatigue</td>
<td>3 weeks</td>
<td>pericarditis</td>
<td>none</td>
<td>improved</td>
</tr>
<tr>
<td>16</td>
<td>26, M, UC</td>
<td>-</td>
<td>fever, dyspnea, cough, fatigue</td>
<td>1 month</td>
<td>pleuritis</td>
<td>methylprednisolone (30mg/day)</td>
<td>improved 12days later</td>
</tr>
<tr>
<td>17</td>
<td>27, F, UC</td>
<td>sulphasalazine (mesalazine) (enema) (suppository)</td>
<td>fever, chest pain</td>
<td>2 weeks</td>
<td>pleuritis</td>
<td>none</td>
<td>improved</td>
</tr>
<tr>
<td>18</td>
<td>20, F, UC</td>
<td>-</td>
<td>chest pain, cough</td>
<td>3 weeks</td>
<td>myopericarditis</td>
<td>methylprednisolone (40mg/day)</td>
<td>improved 3 days later</td>
</tr>
<tr>
<td>19</td>
<td>60, F, UC</td>
<td>-</td>
<td>fever, chest</td>
<td>several years</td>
<td>pleuropersicarditis</td>
<td>methylprednisolone</td>
<td>improved 2 days later</td>
</tr>
</tbody>
</table>

IBD: inflammatory bowel disease
CD: Crohn’s disease
UC: ulcerative colitis

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

References