Pulmonary Infiltration and Eosinophilia Associated with Sulfasalazine Therapy for Ulcerative Colitis: A Case Report and Review of Literature

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We report a 52-yr-old man with ulcerative colitis who developed sulfasalazine-induced pulmonary infiltration with eosinophilia (PIE syndrome), which resolved completely after withdrawal of this drug. Desensitization to sulfasalazine was successful, and allowed the patient to receive this drug without recurrence of the pulmonary toxicity. This is the first case of the sulfasalazine-induced PIE syndrome in Japan; a review of the world literature found no previous cases of successful desensitization following sulfasalazine-induced PIE syndrome.

Key words: PIE syndrome, desensitization

Introduction

Sulfasalazine, a therapeutic agent widely used for inflammatory bowel disease, frequently causes such side effects as nausea and vomiting, skin rashes, fever, headache, blood dyscrasias, and hepatic dysfunction. Pulmonary infiltration and eosinophilia (PIE syndrome) due to sulfasalazine have rarely been reported. We recently encountered a patient who developed PIE syndrome after the start of sulfasalazine therapy. Desensitization to sulfasalazine was successful, and therapy could be restarted without recurrence of the PIE syndrome.

Case Report

A 52-yr-old male nonsmoker developed diarrhea and melena for several days in July 1988. He consulted a medical college hospital, but no abnormalities were found in blood tests or stool examination. He was later admitted to another medical college hospital for an operation due to finger trauma in August 1988. After this hospitalization, bloody diarrhea with tenesmus and abdominal pain appeared again. Oral anti diarrheal agents were given, but his symptoms continued and fever developed. He was then referred to our hospital with suspected inflammatory bowel disease on September 28, 1988. On admission, his body temperature was 38.0°C and pulse was 84/min, and tenderness was observed in the umbilical region with watery and bloody diarrhea. Laboratory data on admission revealed a mild leukocytosis with a normal differential, an elevated C-reactive protein (CRP), and hypoalbuminemia indicating his malnutritional state (Table 1).

A double-contrast barium enema and total colonscopic examination revealed multiple ulcers, pseudopolyps, edema of the colonic mucosa and submucosal bleeding, which were consistent with moderately active ulcerative colitis (Figs. 1, 2). Chest roentgenogram on admission showed no abnormalities. Blood and sputum culture for bacteria and fungi were negative.

A diagnosis of ulcerative colitis was made on the basis of the clinical symptoms together with the barium enema and colonscopic findings. Treatment with sulfasalazine (3.0g/day) was initiated on October 3 with total par enteral nutrition for the first 2 wk. No other medication was prescribed. Fever and melena subsided immediately and diarrhea disappeared in a month. White blood cell count and CRP were normalized. Remission of ulcerative colitis was confirmed by colonoscopy on November 8 (Fig. 3). About 30 days after the initiation of sulfasalazine
therapy, however he complained of a productive cough and slight fever. Laboratory examination revealed leukocytosis with eosinophilia (2,700/mm³). Numerous eosinophils frequently contained 3 or 4 nuclear lobes (Fig. 4). The erythrocyte sedimentation rate was 90 mm in the first hour and the CRP was 5.0 mg/dl, although these tests had returned to normal 2 wk previously. Sputum culture was negative again, but a chest roentgenogram revealed diffuse infiltrative opacities involving both upper lung fields and the left lower lobe (Fig. 5). Pulmonary function tests revealed no restrictive or obstructive patterns. The lymphocyte stimulation test was negative for sulfasalazine. Bronchoscopic examination

![Image 1](Image1.png)

**Fig. 1.** Double contrast film of descending colon demonstrating diffuse granularity with symmetric narrowing and loss of haustra.

![Image 2](Image2.png)

**Fig. 2.** Colonoscopic view of the sigmoid colon on admission demonstrating granular appearance with variable sized ulcerations and no normal appearing mucosa.

![Image 3](Image3.png)

**Fig. 3.** Colonoscopic view of the descending colon on remission demonstrating inflammatory polyps, disappearance of ulcerations and dry appearing mucosa.
was not performed because of the patient's refusal.

A presumptive diagnosis of the PIE syndrome was made from the physical examination findings, laboratory data, chest roentgenogram, and negative culture results. Sulfasalazine was discontinued on December 7, 1988, and oral tranilast (300 mg/day) was given. Over the next 6 days, a dramatic improvement was observed. Cough and dyspnea subsided, and the fever was resolved. A chest roentgenogram obtained 2 wk later was clear except for linear infiltrates in the left lower lobe. The peripheral eosinophilia was also improved. He left the hospital on December 13, 1988.

He had a relapse of ulcerative colitis a month after discharge from the hospital. Accordingly, we tried desensitization to sulfasalazine with the patient's informed consent because sulfasalazine was useful for maintenance therapy and this patient had impaired glucose tolerance. The dose of sulfasalazine was increased slowly over 10 wk as follows: 5 mg/day, 10 mg/day, 20 mg/day, 50 mg/day, 100 mg/day, 250 mg/day, 500 mg/day, 750 mg/day, 500 mg b.i.d., and 500 mg t.i.d. A remission of ulcerative colitis was obtained about 2 months after reintroduction of sulfasalazine. There was no recurrence of the PIE syndrome after the desensitization of sulfasalazine.

Discussion

Ulcerative colitis is generally recognized to be associated with various extra-intestinal complications. Pulmonary vasculitis, suppurative bronchiectasis (1), and bronchial epithelial change (2) have been reported in patients with ulcerative colitis. Therefore, these other lesions must be considered in patients with ulcerative colitis. The differential diagnosis was made easily in this case by the rapid improvement seen after discontinuation of sulfasalazine.

Sulfasalazine-induced pulmonary disease is unusual despite the frequent use of this drug for inflammatory bowel disease. This patient had the typical features of the most characteristic form of sulfasalazine-induced pulmonary toxicity, "PIE syndrome," which is still rare; only 12 cases have been reported including the present case (3–13) (Table 2). The clinical picture is characterized by cough, dyspnea, fever, bilateral lung infiltrates, and peripheral eosinophilia of over 1,000/mm³. The average age of these patients was 43.8 yr, which is higher than usual for inflammatory bowel disease patients. Ten were male, and only 2 were female. The dose of sulfasalazine ranged from 1.0 to 6.0 g/day, and was over 3.0 g/day in most cases. The average period of administration was 9.0 wk, except in 2 cases where the PIE syndrome developed after a very long period of therapy. The prognosis of this syndrome is generally good, and the symptoms quickly were resolved when sulfasalazine was discontinued in all except one fatal case (9).

Sulfasalazine is metabolized into 5-aminosalicylic acid and sulfapyridine, and either of these metabolites may produce the PIE syndrome by a mechanism that remains unknown. Probably the mechanism is, as suggested in an editorial by Gell and Coombs, a type I or type III hypersensitivity reaction (14). The percentage of peripheral eosinophils with three-lobed nuclei was increased in this patient (23% vs 10.5 ± 1.9% in 10 healthy controls), and eosinophils with four-lobed nuclei, which are never observed in healthy controls, were also detected. These hyperactive and hypermature eosinophils may be produced by various stimuli, like eosinophil chemotactic factor in the PIE syndrome (15).

In Japan, most recorded cases of PIE syndrome are due to unknown causes (76.9%), followed by mycosis (19.4%) and parasitism (1.9%) (16). Only 11 cases have
Table 2. Reported Cases of Sulfasalazine-induced PIE Syndrome

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Dose (g/day)</th>
<th>Duration (weeks)</th>
<th>Symptoms</th>
<th>Chest X-ray</th>
<th>Eosin. (/mm³)</th>
<th>Histol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones &amp; Malone (1972)</td>
<td>36</td>
<td>F</td>
<td>4.0</td>
<td>10</td>
<td>Cough, dyspnea</td>
<td>Lt. lung, Rt. upper lobe inf.</td>
<td>1,090</td>
<td>—</td>
</tr>
<tr>
<td>Todd &amp; Dyer (1979)</td>
<td>58</td>
<td>M</td>
<td>1.5–3.0</td>
<td>12</td>
<td>Dyspnea, cough, fever</td>
<td>Bil. confluent opacities</td>
<td>5,590</td>
<td>—</td>
</tr>
<tr>
<td>Constantinidis (1976)</td>
<td>23</td>
<td>F</td>
<td>?</td>
<td>104</td>
<td>Dyspnea, cough, weight loss</td>
<td>Bil. soft inf.</td>
<td>1,008</td>
<td>—</td>
</tr>
<tr>
<td>Berliner et al (1980)</td>
<td>40</td>
<td>F</td>
<td>2.0–4.0</td>
<td>6</td>
<td>Cough, fever, rash</td>
<td>Peripheral lung inf.</td>
<td>1,200</td>
<td>—</td>
</tr>
<tr>
<td>Yaffe &amp; Korelitz (1983)</td>
<td>43</td>
<td>M</td>
<td>4.0</td>
<td>5</td>
<td>Cough, fever, anorexia</td>
<td>Bil. upper lobe inf.</td>
<td>1,807</td>
<td>Acute &amp; chronic inf.</td>
</tr>
<tr>
<td>Baillie (1984)</td>
<td>57</td>
<td>M</td>
<td>4.0</td>
<td>3</td>
<td>Dyspnea, orthopnea</td>
<td>Bil. peripheral &amp; basal inf.</td>
<td>1,728</td>
<td>—</td>
</tr>
<tr>
<td>Cazzadori et al (1985)</td>
<td>26</td>
<td>M</td>
<td>3.0</td>
<td>28</td>
<td>Chest pain, fever</td>
<td>Bil. inf. opacities</td>
<td>1,100</td>
<td>—</td>
</tr>
<tr>
<td>Sullivan (1987)</td>
<td>40</td>
<td>M</td>
<td>2.0</td>
<td>8</td>
<td>Malaise, fever, cough</td>
<td>Bil. upper lobe inf.</td>
<td>1,500</td>
<td>Bronchiolitis obliteration</td>
</tr>
<tr>
<td>Jordan &amp; Cowan (1988)</td>
<td>26</td>
<td>M</td>
<td>1.0</td>
<td>312</td>
<td>Dyspnea, fever</td>
<td>Collapse</td>
<td>2,709</td>
<td>Consolidation Rt. mid. lobe</td>
</tr>
<tr>
<td>Scherpenisse et al (1988)</td>
<td>36</td>
<td>M</td>
<td>6.0</td>
<td>6</td>
<td>Dyspnea, cough</td>
<td>Bil. lateral Rt. upper lobe dense opacities</td>
<td>1,864</td>
<td>—</td>
</tr>
<tr>
<td>Present case (1989)</td>
<td>52</td>
<td>M</td>
<td>3.0</td>
<td>8</td>
<td>Cough, fever</td>
<td>Bil. upper lobe inf. Lt. lower lobe inf.</td>
<td>3,198</td>
<td>—</td>
</tr>
</tbody>
</table>

Bil., bilateral; inf., infiltration; Rt., right; Lt., left; —, not described; Eosin., eosinophil; Histol., histology.

been described in the literature as being drug-induced, with anti-inflammatory agents, antibiotics, a contrast material, anti-arrhythmic agent, and gold salt being involved (17–27) (Table 3).

Two etiological agents that have been specifically related to the PIE syndrome are parasitic infestation and allergic reactions. In contrast to the decreasing role of parasitism as a cause of the PIE syndrome, drugs and environmental hazards have recently become more significant (28).

Desensitization to sulfasalazine has been attempted for various hypersensitivity reactions, including skin rashes, fever, nausea and vomiting, headache, alopecia, joint pain, facial edema, and hemolysis (9, 11, 29–35). The overall success rate is reported to be better than 77%, but for eosinophilic pneumonia, Sullivan (11) failed to achieve desensitization to sulfasalazine, and therefore used azodisalicylate (Olsalazine) to control the colitis and pulmonary problem. In the light of the experience with the present case, we suggest that desensitization to sulfasalazine is initially attempted for PIE syndrome induced by this drug.

In the present case, of course careful follow-up is necessary so as to detect the recurrence of PIE syndrome or any other side effects in the future. Scherpenisse et al (13) reported the use of Olsalazine for a patient with Crohn’s disease and sulfasalazine-induced eosinophilic pneumonia. For the patients in whom desensitization to sulfasalazine fails, this new 5-aminosalicylic acid compound (Olsalazine) may prove to be a useful alternative.
Table 3. Reported Cases of Drug-induced PIE Syndrome in Japan

<table>
<thead>
<tr>
<th>Drug</th>
<th>First author (yr)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Eosin. (%)</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Nitrofurantoin</td>
<td>K. Kawai (1975)</td>
<td>51</td>
<td>F</td>
<td>12</td>
<td>3,200 U/ml</td>
</tr>
<tr>
<td>2) Salicylates</td>
<td>T. Matsushima</td>
<td>19</td>
<td>F</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Bromovaleryl urea</td>
<td></td>
<td>69</td>
<td>F</td>
<td>56</td>
<td>2,992 U/ml</td>
</tr>
<tr>
<td>Nonfuramin</td>
<td></td>
<td>50</td>
<td>F</td>
<td>29</td>
<td>2,299 U/ml</td>
</tr>
<tr>
<td>5) D-Penicillamine</td>
<td>S. Hayashi (1985)</td>
<td>42</td>
<td>F</td>
<td>33</td>
<td>Normal</td>
</tr>
<tr>
<td>6) Gold salt</td>
<td>Y. Takiguchi (1985)</td>
<td>50</td>
<td>F</td>
<td>1</td>
<td>↑</td>
</tr>
<tr>
<td>7) Rifampicin</td>
<td>A. Kinoshita (1985)</td>
<td>77</td>
<td>M</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Imipramine HCl</td>
<td>M. Irie (1987)</td>
<td>37</td>
<td>F</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>9) Minomycin</td>
<td>S. Morita (1987)</td>
<td>59</td>
<td>M</td>
<td>1</td>
<td>↑</td>
</tr>
<tr>
<td>11) Serrapetase</td>
<td>T. Igiishi (1988)</td>
<td>51</td>
<td>M</td>
<td>1</td>
<td>↑</td>
</tr>
</tbody>
</table>

Eosin., eosinophil; ↑, increased; –, not described.

References

25) Morita S, Mitaniyama T, Matsuda Y. A case of PIE syndrome...


