OBSERVATION

Erythema Nodosum–like Eruption as a Manifestation of Azathioprine Hypersensitivity in Patients With Inflammatory Bowel Disease

Anne-Laure de Fonclare, MD; Kiarash Khosrotehrani, MD, PhD; Sélim Aractingi, MD, PhD; Paul Duriez, MD; Jacques Cosnes, MD; Laurent Beaugerie, MD, PhD

Background: Clinical manifestations of hypersensitivity to azathioprine may mimic symptoms of the initial disease. We report 5 cases of peculiar skin hypersensitivity reactions to azathioprine in patients with inflammatory bowel disease.

Observations: In 5 patients with a recent azathioprine regimen, manifestations appeared between 8 and 18 days after drug introduction. All patients had a high fever. Three patients initially had erythema nodosum; 2 patients had sterile pustules. All had elevated neutrophil counts and serum C-reactive protein levels, whereas eosinophil counts were normal, ruling out drug-induced rash with eosinophilia and systemic symptoms. In 3 patients who were rechallenged with azathioprine or with 6-mercaptopurine, dermatological lesions recurred within hours.

Conclusions: Erythema nodosum and pustules are rarely reported manifestations of azathioprine hypersensitivity. Both skin lesions may be related to the clinical activity of inflammatory bowel disease. Relapse of such lesions shortly after thiopurine rechallenge should raise the hypothesis of hypersensitivity rather than pharmacological manifestations.

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Hiopurines are widely used as a maintenance treatment of Crohn disease and ulcerative colitis, as well as in other clinical contexts such as posttransplantation immunosuppressive therapy. The adverse effects reported with this drug have been classified as early events or as late events. Late adverse reactions are dose-dependent cytopenias and can be partly anticipated by evaluation of the patient’s thiopurine methyltransferase activity. Early adverse reactions to azathioprine are common and include hypersensitivity. Unlike IgE-mediated allergy, the clinical manifestations of this systemic idiosyncratic reaction are heterogeneous and include fever, hepatitis, nephritis, pneumonia, hypotension, arthralgias, pancreatitis, pericarditis, digestive symptoms, and skin manifestations. Severe systemic hypersensitivity manifestations are uncommon. To our knowledge, erythema nodosum–like nodules or pustules have not been described as manifestations of hypersensitivity to azathioprine in inflammatory bowel disease. These skin manifestations can be associated with infections or may suggest worsening of the underlying bowel disease. This may lead to life-threatening delays in the diagnosis of hypersensitivity and in the discontinuation of azathioprine treatment. Herein, we describe azathioprine hypersensitivity in 5 patients manifesting unusual skin nodules and pustules.

REPORT OF CASES

The following observations were made in 5 patients (3 men and 2 women) between January 23, 2004, and May 21, 2006 (Table 1 and Table 2). Four patients had Crohn disease, and 1 patient had ulcerative colitis. All patients had levels of thiopurine methyltransferase activity within the normal range. Azathioprine treatment was introduced in all patients as a corticosteroid-sparing agent. The clinical symptoms occurred, on average, 8 to 18 days after the initiation of azathioprine treatment. All patients had high fever (temperature, 39°C) and skin eruption that was localized initially to the lower limbs. Patient 2 and patient 5 had second-
ary extension of the disease to other body parts. In 3 patients (patients 1, 4, and 5), the skin eruptions comprised painful erythematous nodules scattered on the legs that were suggestive of erythema nodosum (Figure, A). In 2 patients (patients 2 and 3), erythematous plaques with superficial pustules or isolated pustules were observed on the legs (Figure, C and D). Other manifestations included joint, abdominal, and muscular pain, with worsening of digestive symptoms in 1 patient (patient 2). Biologically, there was a constant increase in neutrophil counts in all patients, with acute inflammation and high levels of serum C-reactive protein. None of the patients initially had hypereosinophilia. Results of microbiological analyses were negative: cultures of blood, urine, and pustules were devoid of bacteria and fungi. Histological examination of skin biopsy specimens of nodules revealed predominantly septal inflammation of the hypodermis with normal aspects of the epidermis and dermis. In addition, the infiltrate comprised lymphocytes and macrophages with few neutrophils (Figure, B). There was no sign of vasculitis. Analysis demonstrated intraepidermic spongiform pustules containing neutrophils; the surrounding epidermis was also infiltrated with neutrophils (Figure, E and F). No sign of vasculitis was observed in the dermis. In 1 patient (patient 3), hepatitis and pancreatitis were diagnosed (Table 2). The initial suspected diagnoses were infectious disease in 3 patients (patients 1, 3, and 4), digestive disease relapse in 1 patient (patient 2), and hypersensitivity in 1 patient (patient 5). After interruption of azathioprine therapy and initiation of corticosteroid therapy in 2 patients (patients 3 and 1), complete regression of all clinical and biological abnormalities, including neutrophilia, was noted within 2 weeks and persisted afterward. Three patients were rechallenged with azathioprine, the metabolic equivalent 6-mercaptopurine, or both. The rechallenge was scheduled at least 1 month after resolution of the initial symptoms. In all patients, relapse of the initial symptoms occurred within hours. In 1 patient (patient 4), this relapse was complicated by a sharp decrease in blood pressure. Symptoms again resolved within hours after drug withdrawal.

### Table 1. Observations of Hypersensitivity to Azathioprine

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Other Daily Treatment at Initiation of Azathioprine</th>
<th>Azathioprine Initiation to First Clinical Manifestation, Interval, d</th>
<th>Resolution of Clinical Signs</th>
<th>Resolution of Biological Signs</th>
<th>Drugs Used for Rechallenge</th>
<th>Interval Between Rechallenge and Clinical Manifestations, h</th>
<th>Clinical Manifestations After Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/17</td>
<td>Budesonide (12 mg)</td>
<td>14</td>
<td>16</td>
<td>19</td>
<td>6-Mercaptopurine</td>
<td>12</td>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>2/M/32*</td>
<td>Prednisone (70 mg)</td>
<td>18</td>
<td>11</td>
<td>11</td>
<td>Azathioprine/</td>
<td>48/36</td>
<td>Fever, pustular rash/fever</td>
</tr>
<tr>
<td>3/M/24</td>
<td>Budesonide (9 mg)</td>
<td>16</td>
<td>10</td>
<td>13</td>
<td>6-mercaptopurine</td>
<td>48/36</td>
<td>Fever, pustular rash/fever</td>
</tr>
<tr>
<td>4/F/49</td>
<td>Budesonide (9 mg)</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>Azathioprine/</td>
<td></td>
<td>Fever, pustular rash/fever</td>
</tr>
<tr>
<td>5/M/75</td>
<td>Budesonide (6 mg)</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>. . .</td>
<td>4</td>
<td>Fever, hypotension, and erythema nodosum</td>
</tr>
</tbody>
</table>

Abbreviation: Ellipses, not applicable.

*Initial disease was ulcerative colitis. All other patients had Crohn disease.

### Table 2. Diagnosis of Hypersensitivity to Azathioprine

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Signs</th>
<th>Type of Cutaneous Lesions</th>
<th>Skin Biopsy Findings</th>
<th>Circulating Polymorphonuclear Leukocytes Count, $\times 10^9/L$</th>
<th>C-Reactive Protein Level, mg/L</th>
<th>Transaminase Level</th>
<th>Creatinine Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever and rash</td>
<td>Erythema nodosum</td>
<td>Erythema nodosum</td>
<td>9500</td>
<td>0</td>
<td>190</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Fever, rash, and diarrhea</td>
<td>Amicrobial generalized pustulosis</td>
<td>Subcorneal pustules</td>
<td>9200</td>
<td>350</td>
<td>Normal</td>
<td>NA</td>
</tr>
<tr>
<td>3*</td>
<td>Fever, rash, and myalgias</td>
<td>Amicrobial pustular plaques on legs</td>
<td>Erythema nodosum</td>
<td>16 000</td>
<td>0</td>
<td>250</td>
<td>9N</td>
</tr>
<tr>
<td>4</td>
<td>Fever, rash, and arthralgias</td>
<td>Erythema nodosum</td>
<td>Erythema nodosum</td>
<td>8700</td>
<td>100</td>
<td>160</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Fever, rash, and arthralgias</td>
<td>Erythema nodosum</td>
<td>Erythema nodosum</td>
<td>13 000</td>
<td>50</td>
<td>230</td>
<td>1N</td>
</tr>
</tbody>
</table>

Abbreviations: N, times above the upper limit of normal; NA, not available.

*Lipase level was 12 times above the upper limit of normal. Lipase levels for the other patients were unavailable.

We report 5 cases of pustular or erythema nodosum–like eruption associated with high fever (mean tem-
temperature, 39°C) due to azathioprine hypersensitivity. In accord with previous studies, thiopurine methyltransferase activity was not predictive of this type of adverse effect. In the context of initiation of immunosuppressive therapy, the presence of high fever with nodules and pustules was suggestive of acute bacterial or fungal infection that was rapidly ruled out by results of blood cultures.

After the initiation of azathioprine treatment, symptoms occurred in a temporal manner suggesting hyper-
sensitivity. Similarly, the resolution of symptoms after discontinuation of treatment, the relapse after rechallenge, and the short interval between rechallenge and relapse of the symptoms strongly indicated hypersensitivity to thiopurines. The primary reactive compound is probably not azathioprine but a metabolite, as rechallenge with 6-mercaptopurine produced similar manifestations of hypersensitivity.

Hypersensitivity is a well-known complication of azathioprine therapy. Maculopapular rash seems to be the most frequent cutaneous manifestation of drug hypersensitivity. None of the patients in our study met the criteria for drug-induced rash with eosinophilia and systemic symptoms. Although some patients displayed systemic symptoms such as liver or pancreas abnormalities, none had eosinophilia or maculopapular rash. Two patients (patients 2 and 3) had a peculiar pustular rash. As far as we know, azathioprine has not been reported to be responsible for acute generalized pustular exanthematic rash, a well-described type of drug reaction. In patient 3, the pustular rash was distinct from the usual acute generalized pustular exanthematic rash, as it was confined to the lower limbs. To our knowledge, pustular rash and erythema nodosum have each been described only once in association with azathioprine hypersensitivity in situations other than inflammatory bowel disease.

Pustules and erythema nodosum are associated with inflammatory bowel disease. One of our patients initially had a flare of his digestive symptoms, and another patient had inflammatory joint pain. These observations suggest that azathioprine hypersensitivity in some cases may mimic the symptoms of inflammatory bowel disease. Similarly, anterior uveitis, a rare complication associated with inflammatory bowel disease, has been associated with azathioprine therapy in a patient with ulcerative colitis. Azathioprine hypersensitivity has been reported to mimic the initial disease in other disorders such as myasthenia and dermatomyositis. Neutrophilic dermatoses such as Sweet syndrome and pyoderma gangrenosum have been described as secondary to azathioprine therapy in inflammatory bowel disease. Neutrophilic dermatosis may be secondary to a pharmacological effect of azathioprine. The histological findings of the pustular rash with neutrophilic infiltration could be compatible with such a diagnosis. However, histological examination of the nodules did not reveal marked edema or neutrophilic infiltration characteristic of Sweet syndrome. Further, the short interval between rechallenge and relapse of the symptoms at a higher intensity (after a 1-month washout period) indicated an immunological reaction against azathioprine or its metabolites.

In the patients described herein, azathioprine was interrupted because of suggestion of excessive immunosuppression causing infection, inefficiency, or hypersensitivity. After ruling out infection in 3 of 5 patients, it seemed plausible that azathioprine could be reintroduced on the basis that the manifestations were due to inflammatory bowel disease. The findings from our study suggest that hypersensitivity should be considered as an alternate diagnosis and that rechallenge should be avoided or conducted under close surveillance, as we observed a sharp decrease in blood pressure in 1 patient necessitating resuscitation.

Early adverse effects of azathioprine, including hypersensitivity manifestations, seem to be more common in patients with Crohn disease compared with patients with autoimmune hepatitis (29% vs 2% of treated patients). In that study, the significant difference between the 2 groups was independent of thiopurine methyltransferase levels, azathioprine initiation dosage, or simultaneous intake of prednisone. Overall, it seems that patients with inflammatory bowel disease tend to have specific and frequent manifestations of azathioprine hypersensitivity. Whether this particular sensitivity of patients with Crohn disease is genetically determined is unknown. In accord with this hypothesis, recent pharmacogenetic investigations have pointed to other polymorphisms in the metabolic chain of purines that are associated with early adverse effects of azathioprine and 6-mercaptopurine, the inosine triphosphate pyrophosphatase 94C→A polymorphism is related to increased flulike syndrome, cutaneous eruption, and pancreatitis in patients with inflammatory bowel disease.

In conclusion, we demonstrate herein that erythema nodosum–like skin lesions are a potential clinical sign of hypersensitivity reaction to thiopurines. A careful analysis of the timing of exposure to azathioprine and the appearance of erythema nodosum and other signs of hypersensitivity can provide important clues to the underlying cause of this condition. In the clinical situation in which erythema nodosum and other signs of hypersensitivity are present following the introduction of azathioprine, discontinuation of the drug is warranted.

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