Auranofin-Associated Colitis and Eosinophilia

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Gold compounds, often used in the treatment of rheumatoid arthritis, have been associated with gastrointestinal disturbances in some patients. Use of auranofin, an oral gold preparation, in a 50-year-old woman with rheumatoid arthritis resulted in diarrhea, abdominal tenderness, nausea, and vomiting, which persisted despite discontinuation of auranofin therapy. The presumptive diagnosis was gold-induced colitis and eosinophilia. Administration of cromolyn sodium provided relief. Although this complication may be rare, evolving bowel symptoms in patients receiving auranofin demand prompt attention.

Colitis associated with use of parenterally administered gold is a rare but potentially dangerous complication because it may progress to fulminating enterocolitis, toxic megacolon, and death. Accompanying eosinophilia has been found in less than 25% of the reported cases. Auranofin, a recently approved oral gold preparation for treatment of rheumatoid arthritis in adults, has been reported to be associated with colitis in one previous case. Recently, we observed this association accompanied by pronounced eosinophilia in one patient.

REPORT OF CASE

A 50-year-old woman with insulin-dependent diabetes mellitus, Hashimoto’s thyroiditis, and seropositive rheumatoid arthritis participated in an auranofin and d-penicillamine double-blind study for 48 weeks. Because of a satisfactory response, after completion of this study she was entered into a long-term open-label study of auranofin at a dosage of 3 mg twice a day. Three months later, the disease activity intensified and the dosage of auranofin was increased to 3 mg three times a day.

Diarrhea (passage of two to seven stools daily) developed within 2 days but was controlled with diphenoxylate hydrochloride and atropine (Lomotil) and resolved without discontinuation of the use of auranofin. Two months later, the diarrhea recurred and progressively worsened despite discontinuation of auranofin therapy and administration of Lomotil. She required hospitalization a week later because of nausea, vomiting, and watery diarrhea (8 to 10 stools per day) with mucus but no blood.

The patient was afebrile and dehydrated, and she had diffuse abdominal tenderness and hyperactive bowel sounds. The hemoglobin concentration was 14.9 g/dl, and the leukocyte count was 18,600/mm³ with 47% polymorphonuclear leukocytes, 32% eosinophils, 11% lymphocytes, 6% monocytes, 2% basophils, and 2% bands. Two weeks previously, the leukocyte count had been 12,900/mm³ with 1% eosinophils. Stool cultures for bacterial pathogens were negative. Three stool examinations were negative for parasites but showed many leukocytes. An assay for Clostridium difficile was negative. Flexible proctosigmoidoscopy disclosed pale mucosa that lacked the usual vascular markings. Although the mucosa was abnormally friable, no ulcerations were found. Mucosal biopsy specimens from the...
A presumptive diagnosis of gold-induced colitis and eosinophilia was made, and the patient was treated with intravenous fluids and psyllium hydrophilic mucilloid (Metamucil). Because of persistent diarrhea after 5 days of conservative therapy and 2 weeks after use of auranofin was discontinued, she was given cromolyn sodium, 20 mg four times a day as an oral suspension. Her condition improved rapidly, and she was dismissed on the seventh hospital day. The cromolyn sodium regimen was continued for a total of 10 days.

A month later, the patient was free of gastrointestinal symptoms, and the leukocyte count was 13,000/mm³ with no eosinophils. After 12 months of follow-up, she continued to do well and had no further episodes of diarrhea. Her arthritis remained active and was being treated with hydroxychloroquine.

DISCUSSION
Diarrhea can accompany auranofin therapy in 29 to 44% of patients. It is usually mild and necessitates discontinuation of therapy in only 5% of the patients. Auranofin-associated diarrhea usually occurs within a few hours after administration of a dose. Numerous stools may be passed daily and are preceded by abdominal cramping. Nocturnal diarrhea does not occur. Some patients may not experience daily diarrhea, and others may have spontaneous remission of the bowel symptoms. Auranofin-induced diarrhea may develop anytime during the course of therapy but most commonly is observed during the first 3 months. In most cases, no treatment is necessary. The diarrhea may respond to such measures as decreasing the auranofin dose temporarily, increasing the bulk in the stools, or using kaolin with pectin (Kaopectate) or Lomotil. Rarely, use of auranofin must be discontinued.

The pathologic mechanism of auranofin-associated diarrhea is uncertain. Experimental evidence in human volunteers demonstrated no pathogenic flora, occult blood, or steatorrhea. The results of D-xylose, Schilling, and glucose breath tests were normal, as was the stool osmolality. An increase in fecal sodium and water content was demonstrated. In vitro studies of rat small intestine suggested an inhibition of active sodium reabsorption in the intestinal lumen. Further in vivo studies of canine jejunum supported this observation. The in vitro studies of mucosal homogenates of rat small bowel suggested that the mechanism of action was a concentration-dependent auranofin inhibition of Na⁺-K⁺ adenosine triphosphatase. No in vivo effect on canine colonic smooth muscle activity could be demonstrated.

The cause of frank colitis related to either parenterally or orally administered gold is not understood. One hypothesis is that the elemental gold or carrier molecule has a direct toxic effect on the mucosal lining. Alternatively, an immunemediated hypersensitivity reaction may be involved. Mixed lymphocyte stimulation in association with use of gold sodium thiomalate has been noted in one case of gold-induced enterocolitis. In another patient, temporary development of circulating immune complexes has been observed in relationship to the onset of enterocolitis during gold sodium thiomalate therapy.

The clinical manifestations of gold-induced enterocolitis described previously were similar to those reported in our patient: acute abdominal pain, abdominal tenderness, nausea, vomiting, diarrhea, and fever. Unlike our case, most of the other reported cases, including the previous auranofin-associated case of colitis, occurred within weeks after initiation of therapy. Although the colon is most commonly involved, gold-induced enterocolitis has been found histopathologically to involve the esophagus, stomach, and small bowel. We suspect that our patient had other areas of bowel involvement that contributed to the severe diarrhea, which was not expected on the basis of the selective biopsy samples taken at the time of sigmoidoscopy. The severity of her illness and the lack of response to initial discontinuation of the auranofin therapy suggest the likelihood of gold-induced enterocolitis rather than the presence of simple auranofin-related diarrhea.

Because of the paucity of reported cases of gold-induced enterocolitis, conclusions cannot be formulated about the efficacy of any therapeutic modality beyond discontinuing the compound.
and instituting supportive measures. Administration of corticosteroids and the chelating agent dimercaprol have yielded varied results. Our empirical oral use of cromolyn sodium was based on one previous report by Martin and associates in another case of colitis associated with blood eosinophilia. The rationale for its use is to prevent the release of vasoactive amines from mast cells in the bowel wall. In the previous report, as well as in our case, a close temporal relationship was noted between the initiation of cromolyn therapy and the alleviation of the diarrhea.

Routine eosinophil counts have little utility during the monitoring of oral gold therapy because eosinophilia develops in only 13% of patients taking auranofin. An eosinophil count by itself is not a strong predictor of possible toxicity inasmuch as only 30% of patients who experience a side effect from auranofin have eosinophilia. In the setting of eosinophilia with a potential drug reaction, especially a mucocutaneous one, however, there may be as high as a 75% likelihood that auranofin is the underlying cause. Therefore, determining the eosinophil count during evaluation of a possible toxic reaction is useful.

Although preliminary reports suggest that the type of reaction experienced by our patient is very rare, prompt attention to evolving bowel symptoms in patients taking auranofin is necessary.

REFERENCES