Case report

Gold colitis induced by auranofin treatment of rheumatoid arthritis: case report and review of the literature

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SUMMARY  A case of ulcerative colitis occurred during treatment of rheumatoid arthritis with the new oral gold preparation auranofin after a cumulative dose of 2160 mg. A barium enema showed loss of mucosal pattern and a rectal biopsy disclosed deep erosions, mucosal inflammation, and crypt abscesses. Precipitates of gold were seen in the periglandular stroma. On electron microscopy the gold deposits seemed to be identical to granules described in gold nephropathy. As the extrapolated serum gold level was within the normal range at the onset of the complication, the morphological findings suggested a local toxicity of the drug. The patient recovered within 14 days of withdrawal of auranofin and the start of therapy with sulphasalazine and steroids. A review of the published work shows that the previously reported mortality in gold colitis of 40% has decreased in recent years. The causes of this decrease may be both the earlier diagnosis of gold colitis and the improved intensive care of its severe complications.

Key words: ulcerative colitis, gold therapy—complications.

Gold salts are effective as slow acting antirheumatic drugs in rheumatoid arthritis, but treatment must be interrupted in 14–53% of the patients because of side effects.1-3 Drug colitis is known as a rare, but frequently fatal, complication of gold therapy.4 Since its introduction in 19765 the new oral gold compound auranofin has proved its efficacy in rheumatoid arthritis.6-8 Side effects seem to be fewer and less severe than those seen with the intramuscular gold preparations.4 Two cases of gold colitis, however, have been observed during treatment with auranofin.9 10 We report a further case and discuss some aetiological, immunogenetic, and therapeutic aspects of this complication.

Case report

HISTORY  A 47 year old man had suffered from erosive rheumatoid arthritis since 1979. He had also suffered intermittently from a duodenal ulcer for about 20 years. Otherwise he was well. In particular he did not have any indication of inflammatory bowel disease. Treatment of the rheumatoid arthritis with chloroquine was stopped after two years because of inefficacy. Subsequent gold therapy with aurothiopolypeptide was tolerated for two years without complications but then had to be stopped after a total dose of 1200 mg because of dermatitis and eosinophilia in the peripheral blood (8%). Treatment was changed to the oral gold preparation auranofin with 3 mg twice daily for nine months, and later 3 mg three times a day, without side effects. He also took 300 mg ranitidine twice daily and 100 mg diclofenac intramuscularly every second day. After 11 months and a total dose of 2160 mg auranofin the patient suddenly developed mucous and bloody diarrhoea with six to seven stools a day, accompanied by abdominal pain and tenesmus.

CLINICAL EXAMINATION  Examination showed the typical joint deformities of rheumatoid arthritis. The abdomen was tender on palpation in the left lower quadrant. Otherwise no pathological findings were detectable.
D I A G N O S T I C  F I N D I N G S

Laboratory investigations showed an eosinophilia of 9% in the peripheral blood but were otherwise normal. Rectosigmoidoscopy was performed after one week and showed intensive reddening and oedema of the mucosa with shallow ulceration and purulent deposits. A barium enema (Fig. 1) showed absent haustration in the descending and transverse colon with irregular gut contours. Histology of a rectal biopsy specimen showed erosions of the mucosa, a dense inflammatory infiltration of the lamina propria with polymorphonuclear neutrophil granulocytes, eosinophils, lymphocytes, plasma cells, and histiocytes (Fig. 2), and numerous cryptal abscesses (Fig. 3). Staining for gold showed punctate black precipitates immediately under the base of the glands and in the periglandular stroma (Fig. 4). Similar changes could not be observed in controls from five other patients with chronic inflammatory bowel disease. Electron microscopic investigation showed a number of phagocytotic cells within the mucosal stroma containing numerous lysosomal osmiophilic cytoplasmic structures (Fig. 5). Some inclusions were surrounded by a thin membrane, others lacked membranes and displayed...
Fig. 4 Rectal mucous layer in auranofin induced colitis. Isolated and complex deposits of dark precipitations in macrophages within the interstitial tissue. Demonstration of gold according to Borchardt-Michaelis.

Fig. 5 Macrophagic interstitial cell in the rectal mucous membrane in gold colitis. Numerous lysosomal and granular structures in the cytoplasm. Location is the same as that shown in Fig. 3. Electron microscopy was carried out after initial formol fixation and conventional paraffin technique.

an indistinct periphery (Fig. 6). They measured from 10 nm to 32 nm in size and occurred at the bottom of the mucosal layer together with leucocytes and other non-specific inflammatory cells. These deposits seemed to be identical to granules described in gold nephropathy. The cells corresponded with those demonstrated histochemically (Fig. 4). We presume that these alterations are precipitations of metallic gold in the colonic mucosa due to the auranofin therapy. Serum gold levels were measured seven and eight weeks after the onset of symptoms and were 135 mg/ml and 130 mg/ml respectively. If a half life of two to three weeks is assumed, the serum gold level was within the therapeutic range at the onset of the complication. The HLA type was A2, A23, B27, Bw62, Cw2, Cw3, Dr4.

As HLA-B27 was positive a tomography of the sacroiliac joints was undertaken and showed normal joints.

Therapy and Course
Therapy with auranofin was stopped and treatment was begun with 1.5 g sulphasalazine four times a day and 50 mg prednisone once daily. All symptoms disappeared after 14 days. A control rectosigmoidoscopy was performed after four weeks and showed normal findings. Steroids were reduced slowly and then withdrawn. In the follow up period of one year the patient showed no evidence of a relapse.

Discussion
It cannot be proved definitely that the observed colitis was due to auranofin, but the absence of symptoms of colitis in the past and the rapid
Fig. 6. Part of an interstitial macrophage with granules and vesicles partially surrounded by a thin membrane. Compare this with the histochemically demonstrated deposits in Fig. 3 and the electron photomicrograph in Fig. 4. Electron microscopy was carried out after initial formalin fixation and conventional paraffin technique.

Table 1  Case reports 1935–79

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref.</th>
<th>Year</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Preparation (mg)</th>
<th>Total dose (mg)</th>
<th>Therapy</th>
<th>Outcome</th>
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<td>1935</td>
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<td>F</td>
<td>thioglucose</td>
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<td>Supportive</td>
<td>Died</td>
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<td>1939</td>
<td>33</td>
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<td>thiosulphate</td>
<td>4</td>
<td>Supportive</td>
<td>Recovered</td>
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<td>Anderson</td>
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<td>47</td>
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<td>74</td>
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<td>Kandrac</td>
<td>17</td>
<td>1961</td>
<td>53</td>
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<td>370</td>
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<td>22</td>
<td>1976</td>
<td>45</td>
<td>F</td>
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<td>200</td>
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<td>Stein</td>
<td>23</td>
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<td>57</td>
<td>F</td>
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<td>Szpak</td>
<td>24</td>
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<td>25</td>
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<td>290</td>
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*BAL=British Antilewisite.
Table 2  Case reports 1980-6

<table>
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<tr>
<th>Author</th>
<th>Ref.</th>
<th>Year</th>
<th>Age (years)</th>
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<th>Preparation (mg)</th>
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<td>29</td>
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<td>59</td>
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<td>30</td>
<td>1982</td>
<td>71</td>
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<td>Steroids, subtot. col., tot. parent. nutr.*</td>
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<td>Schmidt</td>
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<td>Present case</td>
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<td>2150</td>
<td>Steroids, sulphasalazine</td>
<td>Recovered</td>
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*Subt. col. = subtotal colectomy; tot. parent. nutr. = total parenteral nutrition.

Consequently, diarrhoea during the first week of the disease should be regarded as diarrrhoea during acute toxic megacolon. Despite the improved prognosis, outcome may be influenced by dietary and other factors. All patients with ulcerative colitis recovered. However, only patients with total parenteral nutrition, therapy, and improvement may be a result of earlier diagnosis and improvement in supportive therapy. Auranofin, however, that among 14 patients (Table 2) the probands have died of this complication, and in other cases the probands have died of other causes.

In our view, the treatment of ulcerative colitis should be based on the use of appropriate therapy, including the use of sulphasalazine, and other appropriate agents. In the group of patients with ulcerative colitis, the use of sulphasalazine and other appropriate agents was associated with a 40% reduction in the risk of death.

The analysis of the data on ulcerative colitis in the group of patients with ulcerative colitis, the use of sulphasalazine and other appropriate agents was associated with a 40% reduction in the risk of death. The analysis of the data on ulcerative colitis in the group of patients with ulcerative colitis, the use of sulphasalazine and other appropriate agents was associated with a 40% reduction in the risk of death.
References


