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.

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Fig. 1 Barium enema one week after the onset of bloody diarrhoea in gold colitis. Loss of mucosal pattern with irregular gut contours and absent haustration in the descending and transverse colon.

DIAGNOSTIC FINDINGS

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. 2 Dense inflammatory infiltrate throughout the stromal layer of the rectal mucous membrane after therapy with auranofin three times a day. So called 'crypt abscesses' and ulcerative lesions as seen in ulcerative colitis.

Fig. 3 Rectal mucous layer after therapy with 3 mg auranofin three times a day. Severe lymphocytic, histiocytic, and polymorphonuclear leucocyte infiltration. Numerous so called crypt abscesses. Loss of goblet cells. Glandular epithelium activated by inflammation.

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.

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,⁶ 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. 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.

Fig. 6 Part of an interstitial macrophage with granules and lysosomes 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 formol fixation and conventional paraffin technique.

response after withdrawal of the drug make other explanations improbable. Furthermore, the patient had not taken other drugs known to cause colitis.¹³ Twenty eight cases of gold induced colitis have been reported, including two cases due to auranofin¹⁴⁻³⁵ (Tables 1 and 2).

The pathogenesis of the complication is unknown. The normal serum gold level in the patient makes overdosing of auranofin as the cause of colitis unlikely. It is known that the efficacy and toxicity of gold therapy are not related to serum gold levels,³⁶⁻³⁸ suggesting that local mechanisms may play a part. The histological demonstration of stainable gold in the colonic mucosa further supports the possibility of local toxicity of the drug. Up to 95% of auranofin is excreted in the faeces,³⁹ resulting in a constant contact of the substance with the colonic mucosa. Diarrhoea frequently occurs in auranofin therapy,^{40 41} probably caused by a reversible defect in intestinal permeability.⁴² Analogously to mechanisms for gold nephritis^{11 12 43 44} it is suggested that in predisposed individuals the constant exposure of the colonic

Table 1 Case reports 1935-79

Author	Ref.	Year	Age (years)	Sex	Preparation (auro-)	Total dose (mg)	Therapy	Outcome
Goldhammer	14	1935	47	F	thiogluco-	240	Supportive	Died
Perry	15	1939	33	F	thiosulphate	4 inj.	Supportive	Recovered
Anderson	16	1940	47	F	thiosulphate	200	Supportive	Died
Kandrac	17	1961	53	F	thiomalate	74	ACTH, steroids, antibiotics	Recovered
Kaplinksky	18	1971	26	F	thiomalate	370	Steroids, BAL*	Recovered
			43	F	thiomalate	380	Steroids, antibiotics	Recovered
Roe	19	1972	56	F	thiomalate	2 months	Steroids	Died
Kaplinksky	20	1973	24	F	thiomalate	250	BAL	Died
			46	F	thiomalate	485	Steroids, antibiotics	Recovered
Gerster	21	1976	50	F	thioprop. sulph	200	Symptomatic	Recovered
Siegmán-Igra	22	1976	45	F	Intramuscular gold	65	Steroids, BAL, total parenteral nutrition	Died
Stein	23	1976	57	F	thiomalate	335	Steroid enemas	Recovered
Sckolnik	24	1979	25	F	thiomalate	250	Steroids, BAL, total parenteral nutrition	Recovered
			77	M	thiomalate	290	Steroids	Died
Szapak	25	1979	41	F	thiomalate	485	No therapy	Recovered

*BAL=British Antilewisite.

Table 2 Case reports 1980-6

Author	Ref.	Year	Age (years)	Sex	Preparation (µg-)	Total dose (mg)	Therapy	Outcome
Fam	26	1980	64	F	thiomalate	2600	Subtotal colectomy	Recovered
Huston	27	1980	50	F	thiomalate	210	Steroids, total parenteral nutrition	Recovered
Martin	28	1981	38	M	thiomalate	320	Supportive	Recovered
Eaves	29	1982	50	F	thiomalate	155	Cromoglycin	Recovered
Sukernik	30	1982	59	F	Intramuscular gold	410	Steroids, sub. col., * tot. parent. nutr.*	Recovered
Jarner	9	1983	71	M	thioglucoase	235	Steroids, tot. parent. nutr.	Recovered
Nagler	31	1983	69	F	Auranofin	168	Steroids, tot. parent. nutr.	Recovered
Reinhart	32	1983	78	F	thioglucoase	485	Antidiarrhoeic	Recovered
White	33	1983	58	M	thiomalate	130	Steroids, sulphasalazine	Recovered
Schmidt	34	1984	66	F	thiomalate	375	No therapy	Recovered
Goebel	10	1985	56	M	thioglucoase	200	Total parenteral nutrition	Recovered
Jackson	35	1986	45	F	Auranofin	10 weeks	No therapy	Recovered
Present case		1986	34	F	thiomalate	70	Steroids, ileostomy	Recovered
		1986	47	M	Auranofin	2150	Steroids, sulphasalazine	Recovered

*subt. col.=subtotal colectomy; tot. parent. nutr.=total parenteral nutrition.

epithelia to the excreted gold may lead to a change in their antigenicity with formation of antibodies against the mucosa and development of ulcerative colitis. Unfortunately investigations of immune complexes were not performed in the rectal biopsy of our patient.

The complication was not associated with HLA-Dr3, the incidence of which is increased in patients with adverse reactions to gold, in particular proteinuria.⁴⁵⁻⁴⁷

Diagnosis may be made by rectosigmoidoscopy with rectal biopsy or by barium enema. A review of the published work shows that the former methods seem to be most effective in diagnosing gold colitis. In the reported cases rectal biopsies were performed 15 times and led to the diagnosis in all cases,^{9 20-24 26-29 32-34} while rectosigmoidoscopy showed the typical picture of ulcerative colitis in seven^{9 20 23 25 26 32 34} and slight alterations in five^{21 22 27 29 33} of 16 cases. The biopsy specimens were normal in four patients,^{24 28 31} Barium enema was negative in six^{22-24 28 29 31} and positive in five patients.^{9 20 26}

After withdrawal of the drug and introduction of sulphasalazine and steroids the symptoms disappeared within two weeks. Other authors have tried several therapeutic regimens, including steroids, British Antilewisite (BAL), sodium cromoglycate, total parenteral nutrition, and colectomy with mixed results (Table 1). In our view the treatment of choice is sulphasalazine as this drug is also effective in rheumatoid arthritis. Some patients remitted spontaneously without further therapy after withdrawal of gold.^{10 25 33} Because of lethal infectious complications due to severe protein losses under the longlasting diarrhoea with hypogammaglobulinaemia and an additional steroid therapy^{20 22} steroids should be used cautiously.

Stein and Urowitz²³ in a review article on drug induced colitis¹³ quote a mortality from gold colitis of 40%. The analysis of reported cases shows, however, that among 14 patients since 1980 none have died of this complication (Table 2). The improved prognosis may be a result of earlier diagnosis and improved supportive therapy, particularly total parenteral nutrition. All patients receiving auranofin recovered, though one patient developed toxic megacolon.⁹ Despite the improved outcome in recent years gold colitis should be regarded as a potentially lethal complication. Consequently, diarrhoea during gold therapy should always be taken seriously and early investigation by rectosigmoidoscopy with rectal biopsy should be undertaken in all suspicious cases.

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