Case Reports

Severe enterocolitis complicating chrysotherapy

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The use of gold therapy in the treatment of rheumatoid arthritis involves, in a considerable number of patients, the danger of toxicity. Most of the complications, such as dermatitis and mouth lesions, are trivial (Davis, 1969). In a smaller percentage, important organs, such as the kidneys, may be affected with a picture of nephritis or the nephrotic syndrome (Silverberg, Kidd, Shnitka, and Ulan, 1970). Bone marrow depression (Prowse, 1954) and neuritis (Walsh, 1970) may also be precipitated. Hepatitis and gastrointestinal complications are, on the other hand, extremely rare (Freyberg 1966). Only isolated instances of severe ulcerative enterocolitis have been described in the literature.

This paper describes two patients with rheumatoid arthritis who developed extremely severe diarrhoea while receiving gold therapy. One of the patients died from her illness, while the other recovered only after many weeks of severe debilitating disease.

Case reports

Case 1, a 46-year-old woman, was first seen in the out-patient clinic with classical rheumatoid arthritis. She had symmetrical involvement of all the joints and subcutaneous nodules which had appeared and increased in size in the previous year. From her past history, it was noted that she had suffered a 3-week episode of bloody diarrhoea 9 years before the appearance of the joint manifestations. Laboratory investigations revealed an erythrocyte sedimentation rate of 105 mm./1st hr (Westergren) and latex-fixation 1:5120 positive. Eight weeks later, after the joint manifestations did not respond to treatment with analgesics, aspirin, amidopyrine, and meticorten 30 mg. daily, chrysotherapy was commenced, using sodium thiomalate (myocrisin) 50 mg. weekly.

Course

Seven weeks later, after receiving 385 mg. of gold, the patient noticed an improvement. The inflammatory

changes had almost disappeared and it was possible to stop the prednisone. After another 2 weeks, when the total gold dosage had reached 485 mg., the patient developed diarrhoea with three to four watery stools a day. The gold was stopped but the diarrhoea continued and even became worse, so that she was having fifteen to twenty purulent watery stools day and night and lost 5 kg. in weight.

She was admitted to hospital where the diarrhoea continued in spite of opiates, corticosteroids, and antibiotics. Both the joint manifestations and the subcutaneous nodules, which had been present before treatment, disappeared completely.

Laboratory investigations

The erythrocyte sedimentation rate had returned to normal but showed severe derangement of serum proteins—albumin 2 g./100 ml., globulin 1.1 g./100 ml. The immunoglobulin values were IgG 450 mg./100 ml., IgM 14 mg./100 ml., IgA 22 mg./100 ml. Latex-fixation dropped to 1:320 and soon became negative. Stool examination showed numerous leucocytes and erythrocytes, 24-hr stool fats 7 to 12 g. in five examinations with stool mass varying between 900 and 1,500 g. in 24 hrs. Sigmoidoscopy showed a congested, bleeding, and friable mucosa with a continuous yellowish exudate from above. Some superficial ulceration was also seen. Stool cultures were negative and parasites were not found.

Barium enema showed a picture compatible with ulcerative colitis (Fig. 1, opposite). X-rays of the small intestine showed marked intestinal hurry, and 30 minutes after the commencement of the examination, the patient excreted large quantities of barium. Biopsy of the rectal mucosa showed rich infiltration of the mucosa and submucosa with granulocytes, eosinophils, and plasma cells (Fig. 2, opposite).

Progress

Later, a clinical picture of hypogammaglobulinaemia manifested itself with severe infection of the skin, and the sclera and cornea of the right eye, and moniliasis of the genital tract, mouth, and rectum.

FIG. 1 Case 1. Severe involvement of colon

Termination

2 days before death, the patient developed a septic fever, *E. coli* was isolated from the blood, and she died after 5 weeks in hospital. Necropsy was not performed because of the opposition of the family.

Case 2, a 24-year-old mother of two children, was first admitted to hospital in May, 1969, with fever and joint pain.

Her past history revealed repeated pharyngeal infections in her youth and infectious hepatitis 10 months before admission. She had never before suffered from diarrhoea. About 2 months before admission, she had developed pain in the temporo-mandibular joints as well as pain, swelling, and limitation of movement in the elbows, wrists, ankles, knees, and proximal interphalangeal joints. Morning stiffness and fever were prominent features.

Examination

Swelling of the wrists and proximal interphalangeal joints was noted as well as effusions in both knees and flexion contractures of the elbows. Subcutaneous nodules were not palpated.

Laboratory investigations

Haemoglobin 9 g. per cent, leucocytes 5,500, thrombocytes 220,000, antinuclear factor negative, latex-fixation

FIG. 2 Case 1. Rectal biopsy: numerous plasma cells in lamina propria. Haematoxylin and eosin, $\times 300$

negative, and erythrocyte sedimentation rate 120 mm./1st hr.

Treatment

On the assumption that the patient was suffering from early rheumatoid arthritis, treatment was commenced with aspirin, amidopyrin, and indomethacin, but the disease progressed and in January, 1970, chrysotherapy was decided upon.

Course

5 weeks later, after a small dose of gold salt (250 mg. sodiumthiomalate in total), all the joint manifestations disappeared, but at the same time, the patient developed more than twenty copious, watery, green stools. Her condition rapidly deteriorated and 10 days later she was admitted to the medical ward in a grave condition. She was cachectic, grossly dehydrated, and confined to bed because of generalized weakness. The prominent laboratory findings were an erythrocyte sedimentation rate of 10 mm./1st hr Westergren, albumin 2.2 g. per cent, globulin 2.5 g. per cent. (which dropped within 3 weeks to 1 g. per cent.), very low gammaglobulins, and on quantitative immunoelectrophoresis IgG 200 mg./100 ml., IgA 25 mg./100 ml., IgM 130 mg./100 ml.

The urine was clear and the faeces negative for pathogenic micro-organisms and parasites. Steatorrhoea was found with 17 g. fat in 24 hrs. On examination with P.V.P. I^{131} , excretion of 8.4 per cent. of the material was noted within 4 days (normal 1 per cent.), a finding pointing to a protein-losing enteropathy. Small bowel x-rays revealed coils with abnormal mucosal pattern, some being narrow with gaps in the mucosa (Fig. 3). Large bowel radiographs showed irregular oedematous mucosa.

Progress

On the assumption that the diarrhoea was connected with the gold therapy, the patient was treated with fluids, plasma, and British anti-Lewisite. The response was very slow and only after 3 months did the diarrhoea cease. At this stage, the patient was still cachectic and the steatorrhoea persisted although serum proteins returned to normal. Gradually she gained weight and strength and at present, 3 years after the appearance of the joint manifestations, the patient is free of both subjective and objective disease involving the joints and gastro-intestinal tract and is in good health.

Discussion

The association of joint disease with ulcerative colitis and Crohn's disease has often been described. In most cases, the intestinal disease precedes the joint manifestations although, in a small percentage, the joint disease may present first. The rate of development of the joint manifestations is associated with the activity of the gastrointestinal symptoms and *vice versa* (McEwen, Lingg, Kirshner, and Spencer, 1962). The two cases presented illustrate a totally different problem: these patients, who suffered from definite rheumatoid arthritis, developed severe diarrhoea while receiving gold therapy and, simultaneously with the presentation of the diarrhoea, the arthritis went into full remission. There must therefore be a connection between gold therapy and gastro-intestinal manifestations.

Gastrointestinal complications of chrysotherapy

FIG. 3 Case 2. Severe involvement of small bowel.

are rare (Freyberg, 1966) and severe enterocolitis almost unknown. We found descriptions in the literature of only three cases of acute enterocolitis, and it is interesting to note that the progression of the disease was identical to that in our patients.

(i) Goldhammer reported a patient who, after receiving 240 mg. of gold, developed extremely severe diarrhoea and died after only 12 days. At necropsy, ulceration and haemorrhages were found throughout the length of the small and large bowel (Goldhammer, 1935).

(ii) Perry (1939) described a 33-year-old patient with systemic lupus erythematosus who, after five injections of gold, developed copious diarrhoea with forty stools a day. She lost 31 kg. in weight within a few weeks and, irregularity of the colonic, caecal, and terminal ileal mucosa were demonstrated radiologically. She recovered completely after a few weeks of diarrhoea.

(iii) The third case was described by Anderson and Palmer (1940); a 47-year-old woman with rheumatoid arthritis, after 200 mg. of gold, developed severe diarrhoea with more than twenty watery stools a day. This patient also died and, at necropsy, numerous ulcers were found which had penetrated into the submucosa in the ileum and throughout the length of the colon.

A necropsy was not performed on our patient who died, but it is definite that both terminal cases suffered from an acute inflammatory process involving the whole length of the small and large bowel (Fig. 3) which caused severe diarrhoea as well as malabsorption and a loss of protein from the surface of the bowel. The hypoproteinaemia and in particular hypogammaglobulinaemia may be explained by the severe protein-losing enteropathy; the presence of many plasma cells in the biopsy out of Case 1 (Fig. 2) negates the possibility of hypogammaglobulinaemia

as a result of decreased production. The damage in these patients was not caused by large quantities of gold but was possibly a toxic effect as a result of hypersensitivity. Neither of the patients received large doses and in neither did the total dose exceed 500 mg. Likewise, examination of the tissues revealed only small quantities of gold. It is interesting to note that both our patients, like the three described in the literature, experienced a total remission of joint manifestations.

It is not clear whether the remission is associated with the decrease in protein, and in particular in immunoglobulin levels, in these patients or is unrelated and may be regarded as a desirable effect of the gold comparable to the remissions obtained with larger doses. Our case 2, the remission of the joint disease lasted 4 years after the termination of the injections and the intestinal disease.

Although no definite conclusions may be drawn it should be emphasized that Case 2, who recovered completely, began receiving treatment with British anti-Lewisite immediately, while the other did not.

Summary

Two patients with classical and definite rheumatoid arthritis who developed extremely severe diarrhoea while receiving gold therapy are described.

Clinical and laboratory hypogammaglobulinaemia developed in both patients and was the cause of death of one of them; the other recovered after months of debilitating disease. Three similar cases were traced in the literature. Although rare, this enterocolitis should be regarded as a complication of chrysotherapy.

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