Gold induced enterocolitis complicated by cytomegalovirus infection: a previously unrecognised association

V Wong, J Wyatt, F Lewis, P Howdle

Enterocolitis is a rare complication of treatment with gold salts. It was first described in 1935 by Goldhammer and since then only 21 cases have been described. Different treatment regimes including intensive supportive care with a combination of antibiotics, steroids, dimeracrol and disodium cromoglycate have produced variable success. No other concomitant infective agents have been implicated in the course of the disease to date. We report a case of gold induced enterocolitis complicated by cytomegalovirus (CMV) infection that responded to treatment with intravenous gancyclovir.

Case report
A 44 year old housewife with severe seropositive rheumatoid arthritis was unresponsive to treatment with simple analgesia, non-steroidal anti-inflammatory agents (NSAIDS), hydroxychloroquine, D-penicillamine, and salazopyrine. Gold treatment was therefore commenced. She was given a test dose of 10 mg intramuscular gold (myocrisin) with no major side effects. Fortnightly intramuscular injections of 50 mg myocrisin were administered over the next three months. She developed a mild watery diarrhoea after two months of treatment but this resolved after gold injections were temporarily stopped. Further gold treatment was recommenced two weeks later and she received a total dose of 372.5 mg. Her rheumatoid disease activity responded well clinically. Unfortunately two weeks after her last gold injection she presented acutely complaining of lethargy, anorexia, weight loss (9.5 kg), abdominal pain, and watery diarrhoea (up to 20 times per day) with a small amount of blood. She was admitted immediately and no further gold treatment was given. She was not taking any other medication. She or the family had no history of colitis. She also had a three to four week history of a productive cough with greenish sputum.

On examination she was unwell with a pyrexia at 38°C, a tachycardia, and chest signs consistent with a left basal pneumonia. Her rheumatoid arthritis was quiescent and remained so throughout her hospital admission. Her abdomen was generally tender and rectal examination showed watery stool stained with mucus and a small amount of blood. Rigid sigmoidoscopy showed pronounced diffuse inflammation with multiple superficial ulceration and a biopsy confirmed severe proctitis (Fig 1). She showed some response to treatment with supportive measures – namely, oral 20 mg prednisolone daily in a reducing dose and ampicillin. There was a reduction in her stool frequency, an improvement in her abdominal pain, and a less productive cough. She was discharged after one week but four weeks later, she relapsed with symptoms of watery diarrhoea and fresh blood, abdominal pain, and a further weight loss of 6.3 kg. Also, her productive cough had persisted. Her only medication was dihydrocodeine. On examination she was moribund and dehydrated. She was apyreal and a maculopapular rash was present on her arms. Chest examination showed left basal crepitations and her abdomen was diffusely tender but bowel sounds were present. Moderate peripheral leg oedema was also noted.

INVESTIGATIONS
Full blood count showed 12.2 g/100 ml haemoglobin, white cell count, 11.3 x 10^9/L with 89% neutrophils and no eosinophils, and platelet count 410 x 10^9/L. C-reactive protein concentration was 75 mg/l (normal < 10 mg/l). Urea and electrolytes gave a 121 mmol/l serum sodium, 5.6 mmol/l potassium, 5.6 mmol/l ura, and 96 umol/l creatinine. Liver function tests showed normal bilirubin and transaminases but raised alkaline phosphatase at 1062 IU/l (normal <300 IU/l). Serum albumin concentration was 22 g/l. Urinalysis showed proteinuria and 24 hour urinary protein concentration was 0.4 g/l. A chest X-ray film showed left basal shadowing consistent with infection and an abdominal X-ray

Figure 1: Low power view of initial rectal biopsy. There is pronounced variability in the severity of proctitis with total destruction of glands in some areas and very distorted glandular architecture with regenerative atypia in others. Clumps of endocytic cells mark the previous position of mucosa glands (arrows). Haematoxylin and eosin; original magnification ×14.

Academic Unit of Medicine, St James’s University Hospital, Leeds
V Wong
P Howdle

Department of Histopathology, St James’s University Hospital, Leeds
J Wyatt

Academic Unit of Pathology, University of Leeds, Leeds
F Lewis

Correspondence to: Dr P Howdle, Academic Unit of Medicine, St James’s University Hospital, Leeds LS9 7TF.

Accepted for publication 20 October 1992
HISTOLOGY
Initial rectal biopsy and subsequent ileal and colonic biopsies at colonoscopy before treatment all showed similar features (Figs 1 and 2). There was a severe proctocolitis and ileitis with glandula distortion and surface ulceration. This was variable with some biopsies showing very florid regenerative features (Fig 2A). Eosinophils were not evident in the inflammatory cell infiltrate. A prominent feature was the surviving aggregates of endocrine cells marking the former position of glandular bases where colonic crypts had been destroyed (Fig 2B), a feature characteristically seen in graft vs host disease. Also, apoptotic degeneration was frequent within epithelial cells of remaining crypts further increasing the similarity to graft vs host disease. Occasional inclusion bodies highly suggestive of cytomegalovirus were seen in the ileal and rectal biopsies at colonoscopy and subsequently on the initial rectal biopsy when more sections were examined. Although immunoperoxidase was negative, these inclusions were confirmed as containing cytomegalovirus by DNA in situ hybridisation (Fig 3).

The colonoscopic biopsies at seven weeks (on discharge from hospital), three, and seven months showed a progressive improvement in the proctocolitis although a degree of glandular distortion has persisted throughout. No viral inclusion bodies were seen in biopsies taken after treatment with gancyclovir.

Discussion
This patient developed a severe debilitating
colitis with mainly watery diarrhoea two weeks after stopping a course of parenteral gold treatment with a total dosage of 372.5 mg. The close temporal relation of initial resolution of her watery diarrhoea on stopping her gold treatment and subsequent development of severe enterocolitis on recommencement of taken together with the renal (proteinuria), and skin (maculopapular rash) involvement as well as transient hypo-globulinaemia suggested gold as the primary cause of her colitis. There are few descriptions of the histological features of gold induced colitis, but a preservation of glandular architecture and diffuse inflammatory cell infiltrate sometimes with a prominent eosinophil component are said to be characteristic. Although not showing these features, the colonic and rectal biopsies from our patient showed changes unlike those usually seen in idiopathic inflammatory bowel disease. The striking resemblance to graft vs host disease in our case has been described in cytomegalovirus colitis and its occurrence here in a non-transplant patient shows it to be a true feature of cytomegalovirus colitis. Like others, we found in situ hybridisation to be more sensitive than immunostaining for confirmation of cytomegalovirus infection.

This therefore seems to be a case of cytomegalovirus colitis, rather than ulcerative colitis or simple gold induced colitis, complicating gold induced diarrhoea. Perhaps gold induced immunosuppression contributed to the development of cytomegalovirus infection. Her improvement on gancyclovir and no further relapse over the subsequent year of follow up would fit with this diagnosis. Nevertheless the absence of recurrence during long term follow up will be required to exclude underlying idiopathic inflammatory bowel disease.

Gold salts are highly effective in the management of patients with rheumatoid arthritis, most adverse reactions being mild and reversible. Enterocolitis is one of the rare but potentially fatal manifestations of gold toxicity. The mortality in reported cases is high, varying between 35% and 42% despite intensive supportive treatment in conjunction with the use of antibiotics, steroids, and dimercaprol. There was a reported case of gold induced eosinophilic colitis responding to sodium cromoglycate. Of the survivors, none suffered recurrent symptoms after complete recovery. None was rechallenged with gold. The precise mechanism of gold induced enterocolitis is uncertain but seems to be an allergic reaction to elemental gold as various gold salt preparations have been implicated. All patients except one were women, aged between 24 and 59 years, who received low total doses of gold salts (74-485 mg) before recognition of enterocolitis. Any site in the gastrointestinal tract can be affected, although the colon is the commonest and two cases of colonic perforation necessitating colectomy have been described. Patients with gold induced colitis have diarrhoea as a constant feature. This is usually severe and watery, often bloody, and can last up to three or four months. Other features include fever, nausea, vomiting, abdominal cramps, and, less commonly, skin rashes. Repeated stool cultures for pathogens and parasites are invariably negative. This, as far as we know, is the first reported case of the combination of gold induced and infective colitis.

In view of the extreme severity of gold induced colitis, the diagnosis should be considered in any patient on gold treatment who present with diarrhoea, particularly bloody diarrhoea as in our case. Also, concomitant cytomegalovirus infection should be borne in mind in such circumstances.
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We thank Dr Michael Martin, consultant rheumatologist, St James's University Hospital, Leeds, for his kind permission to report this interesting case.

3 Perry MW. Gold injections and colitis. JAMA 1939; 113: 965.