IgG myeloma presenting as ulcerative colitis

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SUMMARY Two patients who presented with ulcerative colitis are described. Both were found to have evidence of IgG monoclonal gammopathy and Bence-Jones proteinuria. This association has been reported previously only in the presence of myelomatous infiltration of the gastrointestinal tract or in amyloidosis, and hence the cases reported appear to be unique.

Although multiple myeloma may involve several organ systems, symptomatic involvement of the gastrointestinal tract is rare. In a major review of the presenting features of myeloma no mention was made of diarrhoea (Osserman, 1969), but occasional reports have documented gastrointestinal tract infiltration by solitary plasmacytoma and in multiple myeloma (Goldstein and Poker, 1966; Tangun et al., 1975). Conversely, cases have been described in which ulcerative colitis was accompanied by plasmacytosis (Fadem, 1952; Bernstein and Dixon, 1964) or by serum M-components (Röckl et al., 1964).

Two elderly patients presented with profuse bloody diarrhoea. Both were found to have features diagnostic of multiple myeloma. No infiltration of the intestine by atypical plasma cells or amyloidosis was demonstrated. In one instance, the diarrhoea responded to local steroid therapy, while in the other the gastrointestinal symptoms ameliorated during treatment of the dysgammaglobulinaemia with systemic steroids and cyclophosphamide. The purpose of this paper is to document the association of ulcerative colitis and myeloma.

Case reports

CASE 1
A 63-year-old Pakistani man, resident in England since 1969, presented in April 1974 with a six-month history of bloody diarrhoea. Other than evidence of weight loss clinical examination was normal but sigmoidoscopy to 17 cm showed a uniformly oedematous, hyperaemic rectal mucosa with mucus and contact bleeding. A biopsy was taken at 15 cm.

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Investigations

The following investigations were normal: haemoglobin, absolute values for white cell count and differential, serum folate, serum vitamin B₁₂, serum iron and total iron binding capacity, and haemoglobin electrophoretic pattern. However, the ESR ranged from 26 to 51 mm/h.

The blood urea, serum electrolytes, serum calcium, phosphate, alkaline phosphatase, and liver function tests, including total serum protein (85 g/l) and serum albumin (47 g/l), were normal, while the serum orosomucoid ranged from 0·6 to 1·6 g/l (NR 0·3-1·2 g/l).

Stool examinations showed no ova, cysts, parasites or abnormal pathogens; Widal reactions to Salmonella typhi, paratyphi A,B,C, and non-specific Salmonellae and fluorescent antibody tests to Schistosoma mansoni and Entamoeba histolytica were negative. Microscopy of the jejunal aspirate showed no cysts of Giardia lamblia but Escherichia coli was cultured from the fluid.

The results of immunological, histological and radiological investigations are shown in the Table.

The stool, which was fluid and contained blood, ranged in volume from 650 to 1500 ml/day. Although initially normal, faecal fat and lactic acid excretion increased to a mean 35 mmol/day and 55·6 mmol/day respectively. Stool sodium loss and faecal nitrogen excretion were also raised. Xylose and double isotope Schilling tests were normal. A jejunal biopsy showed minor blunting of villi and a slight increase in inflammatory cells but immunofluorescence was normal.

Progress (Fig. 1)

Initially he was given salazopyrine and steroid retention enemata only. However, the total serum IgG level, as measured by radial immunodiffusion,
Table Immunological, radiological, and histological features of cases 1 and 2 at presentation

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*Total serum immunoglobulins were measured by single radial immunodiffusion.

†The amount of paraprotein was estimated by scanning densitometry of the cellulose acetate electrophoretic strip.

‡Monoclonal free light chains were detected by their abnormal reactions on immunoelectrophoresis using specific anti-light chain antisera after first detecting a discrete band on cellulose acetate electrophoresis of concentrated urine.

reached 30 g/l in six weeks with a progressive fall of serum IgA and IgM to 1-25 and 0-20 g/l respectively. Electrophoretic densitometry of the M band also showed an increase to a peak of 26-9 g/l. These rapid changes were consistent with the diagnosis of an IgG myeloma rather than a benign monoclonal gammopathy. He was, therefore, started on cyclophosphamide, 5 mg/kg body weight per day, but, because of leucopenia, it was discontinued for three weeks and then given again at 2-5 mg/kg per day, together with oral prednisolone 40 mg/day. On this combined therapy there was improvement in his diarrhoea, a fall in the serum IgG level, and a reduction in the size of the M band. Fluctuating steatorrhoea persisted and, because of radiological evidence of jejunal diverticulosis and the E. coli in the jejunal aspirate, he was treated with a two-week course of ampicillin. His further course and treatment are shown in Figure 1. Regular follow-up over 18 months has shown no deterioration in his clinical state, although adjustment of the chemotherapy dosage has been necessary from time to time. Usually he is maintained on cyclophosphamide, 100 mg, prednisolone, 5 mg, and salazopyrine, 1 g, daily. On treatment repeated sigmoidoscopy has been normal while rectal biopsies have shown a slight increase in inflammatory cells but no abnormal plasma cells nor any evidence of amyloid.

**Case 2**

A 61-year-old woman presented in January 1974 with a three-year history of weight loss and intermittent diarrhoea of increasing severity. She passed six liquid motions daily, the stool containing blood and mucus. She had not been abroad. Physical examination revealed a thin anaemic woman weighing 37 kg (est ideal wt 45 kg). Abdominal and perianal examination was normal. Sigmoidoscopy to 18 cm showed a granular, oedematous rectal mucosa with mucopus and severe contact bleeding. A biopsy was taken at 13 cm.

**Investigations**

Haemoglobin 9-2 g/dl; MCV 82 µ3; MCH 28-5 pg; WBC 16-6 × 109/l with 80% neutrophils, 14% lymphocytes, 3% monocytes, and 3% eosinophils. ESR 75 mm/h. The serum folate and vitamin B12 were normal. Serum iron 2-5 µmol/l; total iron binding capacity 59 µmol/l.

Blood urea, serum electrolytes, serum calcium, phosphate, and alkaline phosphatase were normal. The serum orosomucoid was increased to between 2-2 and 3-0 g/l.

Stool examination showed no evidence of ova, cysts, parasites or abnormal pathogens.

Results of immunological, radiological, and histological investigations are shown in the Table.

Stool volumes averaged 1300 ml/day. The stool was fluid and contained frank blood. Although faecal fat excretion was normal, the lactic acid excretion was increased to 16-7 mmol/day. Faecal nitrogen and sodium excretions were also increased.
Fig. 1 Response of the IgG myeloma protein and intestinal function to therapy in case 1.

Progress (Fig. 2)
The colitis was treated with salazopyrine and steroid retention enemata and the diarrhoea improved dramatically. No effect was seen on the paraproteinemia but specific treatment was withheld.

In April 1974, she developed a right lower lobe pneumonia. The total serum IgG level was 21.2 g/l, the paraprotein was 15.9 g/l by densitometry, and there had been a significant decrease in serum IgA and IgM levels to 0.31 g/l and 0.15 g/l respectively. The patient was admitted for reassessment in September 1974. There had been no recurrence of diarrhoea or rectal bleeding but for six weeks she had been troubled by a salazopyrine-induced photosensitive eruption on exposed areas. Sigmoidoscopy to 20 cm was normal, a rectal biopsy being taken at 15 cm. The histology of the biopsy was normal. The drug eruption resolved over three months and had not recurred 18 months later. During the follow-up period she has been clinically well and the total serum IgG level has tended to fall, although serum IgA and IgM levels are still suppressed. Free light chains are still present in the urine while electrophoretic densitometric values for the M-band have increased progressively to a level of 24 g/l in February 1976.

Discussion
Both patients fulfil the accepted criteria for the diagnosis of myeloma (Galton and Peto, 1968; Medical Research Council, 1971, 1973). The diagnosis requires two of the following: (1) abnormal plasma cells in the bone marrow, (2) positive radiological findings of myelomatosis, (3) a monoclonal immunoglobulin in the serum, urine or both. Although a skeletal survey in both patients was normal, each had a monoclonal IgG serum para-
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protein with free light chains in the urine and atypical plasma cells in the bone marrow. The major diagnostic question is whether the patients had early multiple myeloma or 'benign' paraproteinaemia secondary to inflammatory bowel disease. Neither patient manifested the clinical and laboratory features of developed or advanced multiple myeloma (Pruzanski, 1976) and it is well recognised that benign paraproteins are relatively common in elderly patients (Zawadzki and Edwards, 1972; Kohn, 1974). The following parameters are most helpful in the differentiation of malignant from benign paraproteinaemia: (1) the absolute concentration of the paraprotein, (2) evidence of increasing serum concentration of the paraprotein, (3) suppression of normal immunoglobulin formation, (4) presence of significant amounts of Bence-Jones proteinuria, (5) a characteristic bone marrow picture, (6) results of the skeletal x-ray survey. The presence of at least three of the laboratory criteria can be regarded as indicative of malignancy (Kohn, 1974).

It has been stated that cytological examination of the bone marrow of a qualitative kind does not give much information regarding the benign or malignant nature of the condition (Waldenström, 1973). Indeed, the appearance of IgG-producing myeloma cells is generally considered to be that of typical, well differentiated or moderately differentiated plasmacytic cells (Azar, 1973). However, quantitative analysis is important and plasmacytosis in excess of 20% is usually an indication of malignancy (Zawadzki and Edwards, 1972).

Immunochromic techniques for the estimation of serum paraproteins, such as radial immunodiffusion, have the disadvantage that a polyclonal antiserum will react differently with various monoclonal proteins. Unreliability is also due to variations in molecular size, formation of complex aggregates, and idiotypic antigenicity (Hobbs et al., 1974). In the present study, total serum immunoglobulin levels were measured by radial immunodiffusion, but the inaccuracy of this method was controlled, as far as possible, by remeasuring previous samples from each patient when a new estimate was requested. The paraprotein was quantitated by
 electrophoretic densitometry (Kohn, 1973). Bence-Jones protein (free monoclonal light chains) was detected by immunoelectrophoresis using specific anti-k or anti-λ antisera. The absence of reactivity with anti-γ chain antiserum excluded renal glomerular leakage of paraprotein as the cause of the monoclonal reactions with the anti-light chain antisera. In both cases, Bence-Jones proteinuria was reported to be present in 'moderate' amounts by a semiquantitative assessment but, in our opinion, the unreliability of available methods does not allow a more accurate absolute quantitation to be made.

There can be little doubt regarding the malignancy of the process in the two cases described. In case 1, the marked plasmacytosis (20%) coupled with the presence of atypical plasma cells showing nuclear immaturity is in keeping with this (Zawadzki and Edwards, 1972; Kohn, 1974) while, in case 2, the marrow picture is unhelpful in excluding reactive plasmacytosis. Both patients had paraprotein levels (by densitometry) of approximately 12 g/l at presentation, but these have risen progressively to values of around 25 g/l. Paraprotein levels in excess of 20 g/l are generally indicative of malignancy (Hobbs, 1967; Zawadzki and Edwards, 1972), as is the progressive rise in paraprotein concentration (Hobbs, 1971; Zawadzki and Edwards, 1972; Kohn, 1974). In case 1, a doubling in the serum concentration of the M-component occurred over the course of a few weeks, while the second patient showed this same feature over an interval of many months accompanied by significant suppression of normal immunoglobulin production. Serum IgA and IgM also showed a downward trend in case 1. The presence of immunosuppression has been stressed as a very valuable diagnostic pointer of malignancy (Hobbs, 1967; Zawadzki and Edwards, 1972; Kohn, 1974). Monoclonal light chain components in the urine are a very ominous sign and have only rarely been observed in benign proteinuria. In both the cases described in this report, there was 'moderate' Bence-Jones proteinuria. In our opinion, these patients had evidence of malignant paraproteinaemia but were detected early in the natural history of myeloma, corresponding to stage I in the clinical staging system proposed by Durie and Salmon (1975). The clinical interest lies in their initial presentations with acute bloody diarrhoea, and the sigmoidoscopic, biopsy, and radiological features of ulcerative colitis.

Haemorrhagic colitis, ileocolitis, and proctitis have been recorded among the gastrointestinal complications of leukaemia (Prolla and Kirsner, 1964), lymphoma (Nugent et al., 1972), and lymphosarcoma (Cornes et al., 1961; Myerson et al., 1974). However, major reviews of proven myelomatosis and other monoclonal immunoglobulin disorders have not included nonspecific proctosigmoiditis as a significant feature of the clinical picture in any patient (Osserman, 1959; Owen et al., 1959; Michaux and Heremans, 1969; Williams et al., 1969; Axelsson and Hällen, 1972; Zawadzki and Edwards, 1972; Talerman and Hajie, 1973). Actual infiltration of the gastrointestinal tract by myeloma cells may occur. In a review of the literature, Goldstein and Poker (1966) recorded 46 cases of plasma cell neoplasia involving the intestinal tract, of which 36 were solitary plasmacytomas and 10 were cases of multiple myeloma diagnosed from necropsy material. Rectal biopsies in our two patients showed no evidence of abnormal plasma cells on routine histology or immunofluorescence. Secondary amyloidosis of the large bowel could also explain the proctosigmoiditis but this was excluded as far as possible by specific staining of the biopsy material. However, this technique does not exclude the possibility of amyloid infiltration of arterioles in the submucous layers (Campbell and Halford, 1964).

Specific documentation of an association between 'myeloma' and colitis is rare. Bernstein and Dixon (1964) reported a patient with ulcerative colitis who was initially diagnosed as having multiple myelomatosis on the basis of a bone marrow plasmacytosis of between 19·5% and 21·5%. There was no radiological evidence of myeloma and no evidence of a monoclonal immunoglobulin in serum or urine. Although this patient would not satisfy the present criteria of myeloma, the absence of a paraprotein might have been due to the relatively unsophisticated methods of serum and urine analysis available at that time. The degree of plasmacytosis seen in their patient is in favour of a malignant process although not diagnostic in its own right (Zawadzki and Edwards, 1972; Kohn, 1974). Röckl et al. (1964) noted that 30-40% of a series of patients with pyoderma gangrenosum also had ulcerative colitis. They investigated six patients and found that four had M-components on electrophoresis. These subjects had increased IgA levels but there was no detailed investigation of the pathological protein. In one patient who died, it was shown that the bone marrow was infiltrated with plasma cells and this patient also had Bence-Jones proteinuria.

Because the aetiology of ulcerative colitis is unknown, it is difficult to speculate about the relationship between the IgG myeloma and the ulcerative colitis in the two patients. Symptoms of colitis have been reported in a few patients with primary humoral immunodeficiency syndromes (Ochs and Ament, 1976). Colitis was associated in some patients with malabsorption, indicating that both small and large intestines were involved,
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whereas the absence of malabsorption in other patients suggests that disease was restricted to the colon (Ochs and Ament, 1976). As IgG myeloma patients have decreased resistance to infection, including that at mucosal surfaces, it is possible that defective local antibody production increases the potential for invasion by hypothetical microorganisms. If this were so, one would expect treatment of the myeloma to be accompanied by improvement in the gastrointestinal disease. This seemed to occur in case 1.

On a practical basis it is suggested that the diagnosis of myelomatosis should be considered in elderly patients presenting with ulcerative colitis.

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