Ulcerative colitis and sarcoidosis

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Summary: Ulcerative colitis is not commonly associated with recognizable pulmonary disease and only four sporadic cases of sarcoidosis in association with ulcerative colitis have been previously reported. However, in a series of 680 patients with ulcerative colitis, pulmonary or extra-pulmonary sarcoidosis has at some stage been present in eight. These cases are reported in detail. The onset of either condition bore no relationship to the activity or the presence of recognized peripheral manifestations of the other, suggesting that the two diseases were independent. However, three of the patients had the HLA B8 DR3 phenotype which is a higher prevalence than seen in previous studies of either disease alone. Patients with ulcerative colitis who possess this HLA phenotype may possibly be more susceptible to developing sarcoidosis.

Introduction

Both interstitial and suppurative broncho-pulmonary disorders have been reported in association with inflammatory bowel disease (Kraft *et al.*, 1976; Eade *et al.*, 1980; Butland *et al.*, 1981; Heatley *et al.*, 1982). In most of the cases described the respiratory conditions appeared to be independent of the intestinal disease and, in general, have been poorly characterized.

Sarcoidosis has some immunopathological similarities with both ulcerative colitis and Crohn's disease (Kraft, 1979; Daniele *et al.*, 1980) but histologically the features more closely resemble the latter condition, primarily because of granuloma formation. Therefore it is not surprising that these two diseases have been noted in association and at times have been difficult to differentiate (Morland, 1947; Dines *et al.*, 1971; Clague, 1972; Padilla & Sparberg, 1972). In contrast, only four sporadic cases of both ulcerative colitis and sarcoidosis have been reported (Trujillo *et al.*, 1967; Jalan *et al.*, 1969; Watson *et al.*, 1972; Theodoropoulos *et al.*, 1981). However, amongst 680 patients with ulcerative colitis currently attending the John Radcliffe Hospital Gastroenterology Unit, features of sarcoidosis have at some stage been present in eight. The details of these cases are reported.

Case reports

Patient 1

In 1959 a 44 year old housewife was diagnosed as having ulcerative proctitis after a short history of

recurrent bloody diarrhoea. Initially she was successfully treated with prednisolone enemas but suffered minor relapses in subsequent years. In 1979 she developed a dry cough with fever, shortness of breath, pleuritic chest pain unresponsive to penicillin, and a one stone weight loss. There were radiological signs of consolidation seen in the right upper lobe, right middle lobe and left lower lobe. A transbronchial lung biopsy revealed a granuloma with a small area of necrosis. Ziehl-Nielsen stains and subsequent culture were negative for tuberculosis. A Kveim test was positive. Her symptoms and radiographic appearances slowly improved without further specific therapy and in 1981 her chest X-ray was normal.

In December 1981 she underwent an emergency colectomy because of a toxic megacolon. Histopathology of the resected specimen was consistent with ulcerative colitis, without evidence of Crohn's disease.

Patient 2

A 31 year old man presented with diarrhoea of 3 months' duration in 1982. Sigmoidoscopy and rectal biopsy were consistent with ulcerative colitis and a barium enema confirmed that the disease was limited to the rectum and sigmoid colon.

A chest X-ray performed in 1981 was normal; however, later in 1982 there was bilateral hilar lymphadenopathy. A Kveim test was positive. Thereafter, he developed a dry cough with mild shortness of breath. Respiratory function tests were consistent with a mild restrictive defect but they returned to normal over the subsequent 9 months without treatment.

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Patient 3

In 1971 a 64 year old retired painter, developed granulomatous iritis and also complained of a localized, irritating area on his scalp. A biopsy of this skin lesion revealed non-caseating epithelioid granulomata without acid-fast bacilli. A chest X-ray was normal. The skin and eye conditions initially responded to topical corticosteroids, but 4 years later the skin lesion had become more extensive. At this time a Kveim test was positive. He was commenced on oral prednisolone 15 mg daily, with which the skin eruption subsided.

In 1978, left upper lobe cavitation was noted. Although sputum culture for *Mycobacterium tuberculosis* and a Mantoux test (1:100) were both negative, he was commenced on rifampicin and isoniazid for 18 months. His cavitation slowly disappeared, leaving fibrotic changes.

In 1983 he developed bloody diarrhoea and anaemia. Sigmoidoscopy and biopsy confirmed active proctitis, a stool culture was negative and a barium enema and small bowel series were both normal. He improved after transfusion, oral prednisolone and sulphasalazine. His chest X-ray remained unchanged in appearance from 1979.

Patient 4

In 1970 a 38 year old housewife developed 2 weeks of fever, myalgia and chest pain. A chest X-ray revealed areas of consolidation in the right and left lower zones, but tomography of the hilar regions was normal. A scalene node biopsy contained numerous granulomata composed of epithelioid cells and multi-nucleate giant cells without necrosis. Culture of this tissue for tuberculosis was negative. The patient clinically improved after an initial course of broad spectrum antibiotics and aspirin at which time a Kveim test was negative. Her chest X-ray was normal 6 months later. She was symptom-free requiring no specific treatment for 6 years.

In 1976 she developed ulcerative proctitis which was diagnosed on the basis of negative stool cultures and histology of a rectal biopsy. A barium enema was normal. Symptoms settled with oral sulphasalazine. However, after one week of this therapy she developed a partial ulnar nerve palsy which did not improve after cessation of sulphasalazine, the introduction of corticosteroid therapy or by nerve decompression one year later at which time a repeat Kveim test was positive. In 1977 she had a mild relapse of her colitis which responded to oral corticosteroids, which she required in low dose for the following 9 months. Since then her ulcerative colitis has been in remission.

Patient 5

In 1964 a 33 year old man developed left sided retinal vasculitis. His chest X-ray revealed an infiltrate in the left mid-zone. No sputum was available for culture, a Mantoux test was negative (1/100) and a Kveim test was positive. Both conditions responded to a short course of oral corticosteroid therapy and have not subsequently recurred.

In 1979 he noted rectal bleeding for the first time. Ulcerative colitis was confirmed on rectal biopsy and a barium enema showed changes distal to the hepatic flexure. The colitis responded to oral corticosteroids and sulphasalazine, and he has had one subsequent relapse which settled with similar therapy.

Patient 6

A 20 year old civil servant presented in 1963 with a short history of bloody diarrhoea, and ulcerative colitis affecting the whole colon was diagnosed. The disease became refractory to medical treatment and he required a proctocolectomy in 1968. The histology of the resected specimen was consistent with ulcerative colitis. At that time a chest X-ray was normal.

In 1979 he developed iritis, followed shortly by the development of a right sided Bell's palsy associated with weight loss of one stone. Splenomegaly and bilateral basal crepitations were noted. A chest X-ray showed patchy consolidation in the right lower and mid-zones with right paratracheal and bilateral hilar lymphadenopathy. A Mantoux test (1:1000) was negative as were sputum cultures for tuberculosis and other pathogens. A clinical diagnosis of sarcoidosis was made. The patient was treated with oral prednisolone without a Kveim test. He initially improved symptomatically and radiologically but abnormal lung function tests were unchanged.

Since then he has been troubled by recurrent urinary calculi associated with hyperoxaluria, hyperuricuria and hypercalciuria. The latter is considered to be associated with sarcoidosis since other causes have been excluded.

Patient 7

In 1971 a 37 year old domestic worker presented with erythema nodosum without apparent cause but a chest X-ray revealed bilateral hilar lymphadenopathy with clear lung fields. A muscle biopsy revealed numerous non-caseating epithelioid granulomata with giant cells. A Mantoux test (1:1000) was negative. A mild microcytic hypochromic anaemia with iron deficiency was noted. Stool cultures were negative for occult blood. The erythema nodosum settled without specific therapy and her anaemia was successfully treated with oral iron. In 1974 her chest

X-ray and haemoglobin had returned to normal.

In 1980 she developed ulcerative proctitis which responded well to prednisolone and oral sulphasalazine.

Patient 8

In 1969 a 47 year old banker developed persistent diarrhoea. Investigations were consistent with a total ulcerative colitis and in 1981 he required a proctocolectomy. Histopathology of the resected specimen confirmed the diagnosis. In 1982 he developed 2 weeks of fever, myalgia and weight loss of half a stone. Hepatosplenomegaly associated with abnormal liver biochemistry were both noted for the first time. A liver biopsy revealed large non-caseating epithelioid granulomas scattered throughout an otherwise normal parenchyma. They were also present in portal tracts but there were no other features of primary biliary cirrhosis. Evidence of tuberculosis was lacking on Ziehl-Nielsen stains and culture of the biopsy. A chest X-ray, early morning specimens of urine and an intravenous pyelogram were all normal. Other known causes of hepatic granulomas were excluded. A Mantoux test was negative (1:1000). An angiotensin-converting enzyme level was elevated (111 IU/l, normal 21–50), but a Kveim test was negative.

Isoniazid, ethambutol and rifampicin were commenced with little clinical response. Nine months later he developed kerato-conjunctivitis sicca. Oral corticosteroids were then added with improvement of symptoms and liver biochemistry.

HLA studies

HLA typing was subsequently performed on all the cases reported. Three patients were HLA A1, B8 and DR3 positive. This contrasts to frequencies of 28%, 21% and 22% respectively for these antigens seen alone in healthy controls or patients with ulcerative colitis without sarcoidosis attending the same clinic (Cottone *et al.*, 1985).

Discussion

The incidence of pulmonary disease in patients with ulcerative colitis is difficult to determine. Johnson *et al.* (1978) reviewed 18 patients with ulcerative colitis and found no evidence of a restrictive disorder more commonly than in 15 controls. However, larger studies have demonstrated an increase in frequency of abnormal pulmonary function (Eade *et al.*, 1980; Heatley *et al.*, 1982). In Heatley's study two patients also had abnormal chest radiographs showing diffuse basal reticulo-nodular patterns. A definitive diagnosis was not made in any of the patients in either study.

Only four sporadic cases of sarcoidosis associated with ulcerative colitis have been reported (Trujillo *et al.*, 1967; Jalan *et al.*, 1969; Watson *et al.*, 1972). In this report of eight such patients from the one gastroenterology unit the diagnosis of ulcerative colitis appeared certain, without evidence of Crohn's disease in any patient. Sarcoidosis is usually a more difficult diagnosis to establish. However, in this series the first five patients had positive Kveim tests together with compatible clinical, radiological and/or histopathological features. Patient 6 was on corticosteroid therapy which would have prevented accurate interpretation of a Kveim test. However, the clinical features make the diagnosis of sarcoidosis almost certain. Patient 7 did not have a Kveim test performed but the combination of clinical features with granulomata in a muscle biopsy also makes sarcoidosis highly likely. The evidence for sarcoidosis would appear the weakest in patient 8. Sarcoidosis is only one of many possible causes of hepatic granulomata (Cunningham *et al.*, 1982), the Kveim test was negative and an elevated angiotensin converting enzyme can occur in other granulomatous conditions (Abboy *et al.*, 1980). However, it is not uncommon for the Kveim test to be negative when sarcoidosis presents in this fashion (Israel, 1983), and none of the other causes of hepatic granulomas were evident. In addition, the patient also developed keratoconjunctivitis sicca and responded to steroids. The presence of liver granulomata has been reported in patients with ulcerative colitis alone but this is exceedingly rare (Perrett *et al.*, 1971).

The Kveim test materials used in this series of patients were not identical, but in all cases were supplied by the Standard Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale, London. Although positive Kveim tests have been noted in some cases of Crohn's disease (Mitchell *et al.*, 1970; Siltzbach *et al.*, 1971), there are no similar reports in patients with ulcerative colitis.

Sulphasalazine sensitivity is a rare cause of pulmonary infiltrates which disappear on cessation of the drug (Yaffe & Korelitz, 1983). Apart from erythema nodosum, no associated extra-pulmonary manifestations or positive Kveim tests have been described. Therefore, it is unlikely that a reaction to sulphasalazine could be incriminated in the pulmonary disorders of patients 1 and 2 who were taking the drug at the time sarcoidosis was diagnosed.

Pulmonary vasculitis has been described in 2 patients with inflammatory bowel disease (Isenberg *et al.*, 1968; Forrest & Shearman, 1975), but granulomas were not a feature in the one case who had a lung biopsy (Forrest & Shearman, 1975). Patient 5 had evidence of retinal vasculitis but the pulmonary infiltrates with a positive Kveim test are much more in keeping with sarcoidosis. Patient 6 had no histopath-

ology to confirm the diagnosis of sarcoidosis or vasculitis. However, the clinical features were strongly in favour of the former. All the other patients had tissue histology compatible with sarcoidosis, without any features of vasculitis.

Although the inflammatory reactions seen in ulcerative colitis and sarcoidosis are very different, immunological factors are important in the pathogenesis of both disorders (Kraft, 1979; Daniele *et al.*, 1980). There is no HLA association with either condition alone (Cottone *et al.*, 1985; Hedfors & Moller, 1972), but patients with sarcoidosis who have erythema nodosum, iritis or a good prognosis more frequently have HLA B8 and HLA DR3 and patients with ulcerative colitis associated with primary sclerosing cholangitis have a high incidence of HLA B8 (Gardner *et al.*, 1984; Brewerton *et al.*, 1977; Chapman *et al.*, 1983). In the current series of patients HLA A1, B8 and DR3 occurred with a higher frequency than has been reported in patients with either disorder alone (Cottone *et al.*, 1985; Hedfors & Moller, 1972).

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