CASE REPORT

Crohn's disease and sarcoidosis in siblings: follow-up of a published report with a new case and brief review of the literature

J M T Willoughby

Lister Hospital, Stevenage,
Hertfordshire

Correspondence to

Dr John Willoughby,
9 Longmeadow Drive, Ickleford,
Hertfordshire SG5 3TJ, UK;
cleveleys69@gmail.com

Received 27 November 2015

Accepted 4 December 2015

Published Online First

4 January 2016

ABSTRACT

Reported in 1971 were the cases of three brothers, two of whom had developed sarcoidosis and the third Crohn's disease. That now presented concerns one brother who, 50 years after the diagnosis and successful treatment of his sarcoidosis, was found incidentally, at colonoscopy performed to exclude malignancy, to have Crohn's colitis in the absence of any symptoms attributable to this. The report concludes with a brief review of the literature.

BACKGROUND

This case represents an opportunity to contribute to the archive of the relationship between Crohn's disease and sarcoidosis an aspect of this that has yet to be reported.

CASE PRESENTATION

Background

In 1955, the eldest of three brothers (patient 1), aged 20, contracted sarcoidosis, with bilateral hilar lymphadenopathy, pulmonary infiltrates, and uveitis. He was treated with oral cortisone and within a year showed no remaining evidence of the disease. In 1957, a second brother (patient 2), aged 21, developed attacks of colicky pain in the right iliac fossa, shown by barium studies after 3 years to be associated with ileal strictures. Ineffectual medical treatment was followed by laparotomy and resection of distal ileum with ileocolic anastomosis. The histology was of a diffuse subacute granulomatous lesion without epithelioid granulomas. In 1967, the third brother (patient 3), aged 22, suffered an attack of right-sided pleuritic pain. A chest film

showed gross enlargement of the right paratracheal and hilar lymph nodes with coarse mottling throughout both lung fields. A lymph node resected at mediastinotomy displayed histological change typical of sarcoidosis. Treatment with prednisolone led to resolution of the pulmonary lesions after 9 months.¹

Patients 1 and 3 have remained free of sarcoidosis after 60 and 48 years, respectively.

Patient 2 suffered no recurrence of Crohn's disease, but in 1989, aged 52, developed abdominal symptoms with progressive weight loss. Colonoscopy was normal, but when he died later that year, autopsy revealed a malignancy of the ileum close to the anastomosis, with diffuse metastases. The primary lesion eluded classification by the British Society of Gastroenterology's panel of histopathologists.

New case

In 2005, patient 1, then aged 70, noted some increase in symptoms he had for years attributed to an irritable bowel with a tendency to constipation, and in view of his age wished to have malignancy excluded as the cause. He therefore underwent colonoscopy in which the only abnormality seen—apart from a small sigmoid polyp—was mild granular inflammation in the transverse colon. The terminal ileum was glimpsed and appeared normal but could not be entered. Microscopy was reported as showing focal inflammation of the lamina propria from the splenic flexure to the caecum, with non-caseating granulomas at all sites except the ascending colon

To cite: Willoughby JMT.
Frontline Gastroenterology
2017;8:74–77.

(figure 1). Subsequent small bowel follow-through examination showed no abnormality. Serum ACE level was 84 IU/L (normal range 10–70). There was no evidence of sarcoidosis in a chest film.

Because of the polyp, colonoscopy was repeated after 5 years, although there had been no change in the mild abnormalities of bowel habit and the patient remained well apart from a recent diagnosis of type 2 diabetes mellitus. Again, the only visible inflammation was in the transverse colon. On this occasion, the terminal ileum was entered, appeared normal, and yielded normal biopsies. Mild focal cryptitis was reported in biopsies from the descending colon to the caecum. Small aggregates of histiocytes were present within the lamina propria, suggesting granuloma formation, although no giant cells were found. There was a lesser degree of change in the sigmoid. In the rectal mucosa, there were occasional foci of granulomatous inflammation.

In retrospect, it seems clear that this patient's Crohn's colitis has been asymptomatic and its duration therefore was impossible to judge. This suggests that in other cases the onset of symptoms may lag the onset of the disease by periods of up to some years.

DISCUSSION

This family, the first to appear in the literature as including members who had contracted either sarcoidosis or Crohn's disease,¹ seems now to be the first on record in which an affected member received also (as many as 50 years later) a diagnosis of the other condition.

In the absence of features indicating recurrent sarcoidosis, the findings on examination of biopsies taken at colonoscopy in this case favoured a diagnosis of Crohn's colitis. The association of Crohn's disease with sarcoidosis in a single patient has been well documented, though not always displaying a clinico-pathological picture in which the two entities were clearly separable. Studied here were 14 patients

chosen as providing evidence strong enough to justify their authors' claim that each diagnosis in the pair could stand on its own as typifying the condition described.^{2–13} In ten, Crohn's disease preceded sarcoidosis.^{3 5–8 10–13} This sequence has given rise to a suspicion that medication for Crohn's disease might be the precipitating cause of sarcoidosis in some cases.^{11 13} In these, it is possible that either the direct action of a drug on the intestinal mucosa or the indirect effect of related change in the local microbiota impaired mucosal defences by a mechanism similar to those that have been identified in studies involving adherent-invasive *Escherichia coli* (AIEC) in Crohn's disease.^{14–16} However, the occurrence of sarcoidosis before Crohn's disease in the remainder^{2–4 9} (to which that now reported should be added) could best be explained by the former originating as in any other case of sarcoidosis, with Crohn's disease following in response to a separate stimulus within the intestinal lumen. It is well established that some form of genetic predisposition is essential to the development of both conditions, rendering individuals so affected abnormally susceptible to the action of one or more environmental agents in precipitating the disease. Because in most cases of sarcoidosis, the diagnosis is suggested by radiological abnormality of the lungs, the hilar lymph nodes or both, the respiratory tract is seen as the most frequent portal of entry for any pathogen commonly acquired by inhalation or toxic particle present in the atmosphere associated with certain occupations.^{17 18} For Crohn's disease, agents considered as potential alternatives to commensal bacteria^{14–16 19} in precipitating onset include various dietary components²⁰ and ingested detergents as contaminants of food.²¹

The fact that both were recognised as 'new' entities by their distinction from tuberculosis has focused on sarcoidosis^{22–24} and Crohn's disease^{25 26} alike a search for mycobacteria as precipitants: a search which has been rewarded with findings that have identified an association without the evidence to prove it causative. From Japan, it has been reported that *Propionibacterium acnes* is the only microorganism to have been cultured from sarcoid lesions, persisting (like the AIEC in Crohn's disease) in a cell-wall-deficient form, which here too was found to provoke a granulomatous inflammatory reaction.²⁷

The difficulty so often experienced by previous authors in separating the two conditions when both seem to have occurred in a single patient has prompted some to hypothesise that Crohn's disease and sarcoidosis may form phenotypically distinct parts of the same disease spectrum.^{28–30} Support for this can be found in studies of gene mutations, some of which show a greater frequency in both conditions than in control subjects.^{31 32} Prominent among these are polymorphisms of the gene NOD2 (nucleotide-binding oligomerisation domain 2) which, when

Figure 1 Colonic biopsy showing chronic inflammation with giant cell in epithelioid granuloma (arrow).

combined with alterations in genes that limit the secretion of pro-inflammatory cytokines in Crohn's disease, can impair the autophagy necessary for the destruction of infected cells and also of the bacteria they contain. Chronic inflammation then follows.^{33–35}

Such changes in the NOD2 gene have also been found to predict the location and course of the disease, being associated with ileal involvement, stenosing and penetrating behaviour, and a complicated course.³⁶ Among patients with sarcoidosis those presenting with Löfgren's syndrome and those with a favourable prognosis have been singled out as possessing the HLA-DBR1*03 allele and the NOD2/CARD15 allotype more frequently than others who progress to a chronic phase.³⁷ Since there is thus no obvious similarity in the prognosis associated with possession of NOD2 alleles in patients with Crohn's disease and sarcoidosis, care should be taken in attributing to these a common role in the pathogenesis of the two conditions. Some associations are non-specific in that they apply to a range of diseases characterised by chronic inflammation, and there remains much uncertainty as to the functional significance of many polymorphisms revealed by genome-wide association studies and other forms of laboratory investigation.^{32 33 38 39} Further research may in time identify one or more genes which are shared by Crohn's disease and sarcoidosis and which could be shown to pose a risk of contracting either.

Cases in which sarcoidosis involves the bowel may closely mimic Crohn's disease clinically, but although there is then usually some thickening of the affected segment, together with the microscopic change of intense granulomatous inflammation, this is rarely transmural, so that typically the gross pathology differs from that of Crohn's disease and does not give rise to the obstruction and fistulation characteristic of the latter.^{30 40} When the presenting symptoms are those of intestinal inflammation, the earliest investigations do not always allow for the possibility that sarcoidosis might be the cause; so that an incomplete history or delay in requesting a chest film showing bilateral hilar lymphadenopathy and/or pulmonary shadowing raises doubt as to whether this was the primary diagnosis or perhaps secondary to the increased permeability of an inflamed intestinal mucosa to some agent capable of triggering sarcoidosis.^{30 40} In one case, it was not until autopsy was performed that sarcoidosis became the preferred diagnosis.⁴¹

The issue of how far the site or sites of a granulomatous lesion should determine its classification came up at a meeting of the American Gastroenterological Association in 1945 when Watson *et al*⁴² presented two cases of extensive small bowel involvement in the presence of a normal chest film as examples of intestinal sarcoidosis. In the subsequent discussion, Crohn refused to accept the diagnosis because neither patient showed the intrathoracic and other features he

considered essential to this. The authors had contended, on the contrary, that regional ileojejunitis was merely sarcoidosis at an atypical site, not a separate entity. In retrospect, these would be seen as classical cases of Crohn's disease, but there remains the question as to whether, in the presence of active intestinal disease with clinically important inflammatory damage to other organs but without strict criteria for sarcoidosis, this could be the diagnosis.²⁸ There is still enough that is obscure in the aetiopathogenesis of chronic granulomatous disease to suggest that today's categories may undergo further subdivision or amalgamation as new findings emerge. Some hint of what developments in the study of genetics may reveal lies in distinctions already observed within both Crohn's disease and sarcoidosis between groups of patients with differing haplotypes.

Current understanding of the relationship between sarcoidosis and Crohn's disease depends in part on their occurrence in different members of the same family, who must share elements of a single genetic constitution. Only four such families appear in the literature,^{1 43 44} and one of those described by Bambery *et al*⁴⁴ is remarkable for the number of well-authenticated cases encountered in two generations and also for the fact that members contracted one or other of the diseases while living in widely separated geographical locations. This speaks for a powerful effect of heredity in both, but the absence of a double diagnosis among at least five affected relatives supports the hypothesis that the genotypes for sarcoidosis and Crohn's disease, though similar, are distinct in some important respect. That this barrier can be overcome in certain circumstances would be suggested by the occurrence of sarcoidosis in patients under treatment for Crohn's disease and the subsequent development of Crohn's disease, as in the patient here reported with a history of sarcoidosis.

The subject in this case was a gastroenterologist with a special interest in inflammatory bowel disease and therefore probably at increased risk of infection with pathogenic microorganisms. His own history of Crohn's disease contracted many years after resolution of sarcoidosis, together with Crohn's disease in one brother and sarcoidosis in another, throws new light on familial susceptibility to both diseases, and in so doing serves to strengthen the evidence for a significant inherited relationship between them.

Acknowledgements My thanks are due to Dr Ian Sargeant for making available the clinical and laboratory details, to Dr Ashish Narula for his advice on the choice of a histology image, to Helen Elwell of the BMA Library Search Services for supplying references to relevant publications, and to Mary James for IT support.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

- 1 Willoughby JMT, Mitchell DN, Wilson JD. Sarcoidosis and Crohn Disease in siblings. *Ame Rev Respir Dis* 1971;104:249–54.
- 2 Morland A. A case of sarcoidosis of the lung with regional ileitis. *Tubercle* 1947;28:32–3.
- 3 Dines DE, DeRemes RA, Green PA. Sarcoidosis associated with regional ileitis (Crohn, 's disease). Report of two cases. *Minn Med* 1971;54:617–20.
- 4 Clague RB. Sarcoidosis or Crohn's disease? *Br Med J* 1972;3:804.
- 5 Padilla AJ, Sparberg M. Regional enteritis and sarcoidosis in one patient. A case report. *Gastroenterology* 1972;63:153–60.
- 6 Oakley JR, Lawrence DA, Fiddian RV. Sarcoidosis associated with Crohn's disease of the ileum, mouth and oesophagus. *J R Soc Med* 1983;76:1068–71.
- 7 James DG, Sharma OP. Overlap syndromes with sarcoidosis. *Postgrad Med J* 1985;61:769–71.
- 8 McCormick PA, O'Donoghue DB, Fitzgerald MX. Crohn's colitis and sarcoidosis. *Postgrad Med J* 1986;62:951–3.
- 9 Fries W, Grassi SA, Leone D, et al. Association between inflammatory bowel disease and sarcoidosis. Report of two cases and review of the literature. *Scand J Gastroenterol* 1995;30:1221–3.
- 10 Friedli A, Musy JP, Umbricht R. Scar sarcoidosis in a patient with Crohn's disease. *Dermatology* 1997;195:276–7.
- 11 Parisinos CA, Lees CW, Wallace WA, et al. Sarcoidosis complicating treatment with natalizumab for Crohn's disease. *Thorax* 2011;66:1109–10.
- 12 Izumikawa K, Motoi N, Takaya H, et al. A case of concurrent sarcoidosis, aortitis syndrome and Crohn's disease. *Intern Med* 2011;50:2915–7.
- 13 Rocha AT, Cabral M, Sad E. Pulmonary sarcoidosis in a patient with Crohn's disease. *Conference abstract. from Publication 142 (4, Suppl 1) American College of Physicians*, 2012.
- 14 Strober W, Adherent-invasive E. coli in Crohn disease: bacterial "agent provocateur". *J Clin Invest* 2011;121:841–4.
- 15 Keita AV, Söderholm JD. Barrier dysfunction and bacterial uptake in the follicle-associated epithelium of ileal Crohn's disease. *Ann NY Acad Sci* 2012;1258:125–34.
- 16 McPhee JB, Small CL, Reid-Yu SA, et al. Host defense peptide resistance contributes to colonization and maximal intestinal pathology by Crohn's disease-associated adherent-invasive *Escherichia coli*. *Infect Immun* 2014;82:3383–93.
- 17 Newman KL, Newman LS. Occupational causes of sarcoidosis. *Curr Opin Allergy Clin Immunol* 2012;12:145–50.
- 18 Tchernev G, Ananiev J, Cardoso JC, et al. Sarcoidosis and molecular mimicry – important etiopathogenetic aspects: current state and future directions. *Wien Klin Wochenschr* 2012;124:227–38.
- 19 Cleynen I, Vazeille E, Artieda M, et al. Genetic and microbial factors modulating the ubiquitin proteasome system in inflammatory bowel disease. *Gut* 2014;63:1265–74.
- 20 Pfeffer-Gik T, Levine A. Dietary clues to the pathogenesis of Crohn's disease. *Dig Dis* 2014;32:389–94.
- 21 Merga Y, Campbell BJ, Rhodes JM. Mucosal barrier, bacteria and inflammatory bowel disease. *Dig Dis* 2014;32:475–83.
- 22 Cowdell RH. Sarcoidosis: with special reference to diagnosis and prognosis. *Q J Med* 1954;23:29–53.
- 23 Richmond BW, Ploetze K, Isom J. Sarcoidosis Th17 cells are ESAT-antigen specific but demonstrate reduced IFN- γ expression. *J Clin Immunol* 2013;33:446–55.
- 24 Chen ES, Moller DR. Etiologic role of infectious agents. *Semin Respir Crit Care Med* 2014;35:285–95.
- 25 Chiodini RJ, van Kruiningen HJ, Thayer WR, et al. Possible role of mycobacteria in inflammatory bowel disease. *Dig Dis Sci* 1984;29:1073–9.
- 26 Wagner J, Skinner NA, Catto-Smith AG, et al. TLR4, IL10RA, and NOD2 mutation in paediatric Crohn's disease patients. An association with *Mycobacterium avium* subspecies paratuberculosis and TLR4 and IL10RA expression. *Med Microbiol Immunol* 2013;202:267–76.
- 27 Eishi Y. Etiologic aspect of sarcoidosis as an allergic endogenous infection caused by *Propionibacterium acnes*. *Biomed Res Internat* 2013; Article number 935289.
- 28 Kiely PD, Rees DH, Axford JS. Crohn's and sarcoidosis. Different manifestations of the same disease process? *British J Clin Pract.* 1994;45:274–5.
- 29 Fellermann K, Stahl M, Dahlhoff K, et al. Crohn's disease and sarcoidosis: systemic granulomatosis? *Eur J Gastroenterol Hepatol* 1997;9:1121–4.
- 30 Brunner J, Sergi C, Müller T, et al. Juvenile sarcoidosis presenting as Crohn's disease. *Eur J Pediatr* 2006;165:398–401.
- 31 Franke A, Fischer A, Nothnagel M, et al. Genome-wide association analysis in sarcoidosis and Crohn's disease unravels a common susceptibility locus on 10p12.2. *Gastroenterology* 2008;135:1207–15.
- 32 Fischer A, Grunewald J, Spagnolo R, et al. Genetics of sarcoidosis. *Semin Respir Crit Care Med* 2014;35:296–306.
- 33 Fritz T, Niederreiter L, Adolph T, et al. Crohn's disease: NOD2, autophagy and ER stress converge. *Gut* 2011;60:1580–88.
- 34 Spalinger MR, Rogla G, Scharl M. Crohn's disease: loss of tolerance or a disorder of autophagy? *Dig Dis* 2014; 32:370–77.
- 35 Strober W, Asano N, Fuss I, et al. Cellular and molecular mechanisms underlying NOD2 risk-associated polymorphisms in Crohn's disease. *Immunol Rev* 2014;260:249–260.
- 36 Cleynen I, Gonzalez JR, Figueroa C, et al. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: Results from the IBDchip European project. *Gut* 2013;62:1556–65.
- 37 Katarzyna B-K, Jaskula E, Wojtowicz A, et al. NOD2/CARD15 genetic variants are associated with susceptibility to Löfgren's syndrome in patients with sarcoidosis. *abstract from Publication 79 482, Tissue Antigens Conference, Liverpool, UK*, 2012.
- 38 Le Bourhis L, Benko S, Girardin SE. NOD1 and NOD2 in innate immunity and human inflammatory disorders. *Biochem Soc Trans* 2007;35:1479–84.
- 39 Lees CW, Barrett JC, Parkes M, et al. New IBD genetics: common pathways with other diseases. *Gut* 2011;60:1739–53.
- 40 Dumot JA, Adal K, Petras RE, et al. Sarcoidosis presenting as granulomatous colitis. *Am J Gastroenterol* 1998;93:1949–51.
- 41 Bulger K, O'Riordan M, Purdy S, et al. Gastrointestinal sarcoidosis resembling Crohn's disease. *Am J Gastroenterol* 1988;83:1415–17.
- 42 Watson CJ, Rigler LG, Wangenstein OH, et al. Isolated sarcoidosis of the small intestine simulating non-specific ileo-jejunitis. *Gastroenterology* 1945;4:30–52.
- 43 Gronhagen-Riska C, Fyrhquist F, Hortling L, et al. Familial occurrence of sarcoidosis and Crohn's disease. *Lancet* 1983; i:1287–8.
- 44 Bamberg P, Kaur U, Bhusnarmath SR, et al. Familial idiopathic granulomatosis: sarcoidosis and Crohn's disease in two Indian families. *Thorax* 1991;46:919–21.