

# Crohn's Disease in Rheumatology Clinic—An Indian Experience

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## ABSTRACT

**Background:** Prevalence of Crohn's disease (CD) among patients with rheumatic illnesses in India is grossly under estimated, especially when it has overtaken that of Ulcerative Colitis in the West.

**Aim:** To study the frequency of histologically unequivocal CD amongst clinically suspected patients with enteropathic arthropathy and to ascertain if the arthritics with CD have any independent clinical predictor.

**Settings and designs:** Retrospective datasheet analysis from a Rheumatology clinic of a large tertiary care centre.

**Materials and Methods:** Patients of suspected enteropathic arthropathy were studied by ileocolonoscopy and segmental colonic biopsy for histological evidence of Crohn's disease and followed up.

**Statistical Analysis:** Logistic regression analysis was done to find out any clinical predictor of histologically proven CD.

**Results:** Fourteen of the twenty-nine patients studied had histologically confirmed CD. Those with CD were younger than those without (34.7 yr vs 41.6 yrs,  $p=0.057$ ). The CD group also had significantly higher number of people with loss of weight (12 vs 1), fever (11 vs 0), perianal fistula (4 vs 0), abdominal pain (8 vs 2), history of dysentery (4 vs 0) and uveitis (6 vs 1) ( $p=0.00002$ ,  $0.00001$ ,  $0.026$ ,  $0.013$ ,  $0.026$  &  $0.01$  respectively). However logistic regression analysis of the most relevant ones among these, namely, loss of weight, fever, and perianal fistula showed loss of weight as only independent predictor of CD in this subset of patients ( $p=0.03$  with odds ratio of 28).

**Conclusion:** Presence of significant loss of weight in an Indian patient with clinically suspected enteropathic arthropathy is an independent predictor of CD.

**KEY WORDS:** Arthritis, Crohn's disease, inflammatory bowel disease, weight loss

Crohn's disease (CD) is being recognized in the West more often over the last two decades.<sup>[1,2]</sup> Up to 25% of patients with CD can have extra intestinal symptoms as its manifestation, arthropathy being the commonest among them.<sup>[3,4]</sup> CD associated with enteric arthropathy can be of spondyloarthropathy (SpA) type,<sup>[5]</sup> Rheumatoid (RA) type,<sup>[6]</sup> a combination of SpA and RA type, oligoarticular, monoarticular, or Jaccoud type arthritis<sup>[7]</sup> and other atypical arthritis.<sup>[8]</sup> Often the arthropathy of CD can accompany, precede, or follow bowel symptoms. Symptoms of arthritis can be the dominant presentation and the bowel symptoms can be very mild.<sup>[9]</sup> In such a situation gastrointestinal manifestation can be considered as a separate entity, both by the patient and the physician.

There is also a lack of awareness regarding CD, as it is considered to be a rare entity in our country and classical cases remain undiagnosed. Although CD was reported in Asian Indians overseas,<sup>[10]</sup> there was no Indian data from India at the

time of the study. We thus looked for histological evidence of CD and its clinical correlates in suspected patients of enteropathic arthritis from our Rheumatology Clinic.

## Materials and Methods

In this retrospective study, patients were selected from the outpatient and inpatient departments of Medicine, Gastroenterology and Rheumatology between September 1996 and August 1998 and thereafter the follow up was recorded from the case sheets till March 2005. Patients included in this study were those of chronic inflammatory arthropathy with chronic abdominal pain, diarrhea, dysentery, perianal abscess and perianal fistula. Those with obvious irritable bowel syndrome or hemorrhoids were excluded after clinical evaluation.

Chronic inflammatory arthritis was defined as arthritis of large, small or axial joints of more than 6 months duration with daily morning stiffness of more than 1 hour or elevated inflamma-

tory parameters like raised ESR or C-reactive protein, in the absence of any obvious infective process.

A detailed rheumatological and gastroenterological examination was done for these patients. Ileocolonoscopy and segmental colonic biopsy were done in those patients who gave informed consent. Histological evaluation of biopsy specimens was done to look for evidence of CD. Endoscopic appearance of CD namely aphthous ulcers, deep or longitudinal fissures, cobble stone appearance, edema, strictures, pseudo polyps, skip areas and rectal sparing of the ulcerative lesions were noted. But histological appearance was taken as the gold standard for diagnosis of CD. Classical histological description of discrete, non-confluent, noncaseating microgranuloma was adopted to define CD. Confluent granulomas with caseation of tuberculosis were differentiated from CD by dedicated gastrointestinal pathologist. The stains used were H&E

All patients were treated with sulphasalazine and or Methotrexate and followed up in our hospital at regular intervals.

The demographic parameters, clinical symptoms and complications were compared between those arthritics with CD and those without. This was done by univariate analysis using Chi square and Fischer's exact test. Subsequently, logistic regression analysis was done among the most relevant parameters to look for any independent clinical predictor for the diagnosis of CD. The software package SPSS was used for regression analysis.

## Results

Of the 32 patients fulfilling the study criteria, ileocolonoscopy and segmental colonic biopsy was done in twenty nine. Fourteen of these 29 patients had histological evidence of CD (Figure 1). Of the remaining, five patients had non-specific chronic colitis without any definite evidence of inflammatory bowel disease, five other had unclassifiable minimal inflammatory

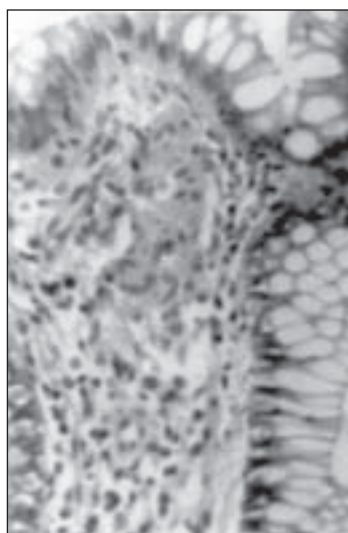


Figure 1: Segmental intestinal biopsy section under light microscope high power magnification. Discrete nonconfluent, non caseating micro granuloma of Crohn, disease

infiltrate, three had possible infective colitis without any identifiable organism and two others were totally normal.

Baseline demographic characteristics of the patients with CD and those without CD are shown in Table 1. Majority of the patients with CD belonged to the eastern and southern part of India. There was however no significant difference in the geographical distribution of patients with or without CD. The CD group patients were of younger age group when compared with those without CD ( $P = 0.057$ ). The mean duration of joint symptoms was 4.6 years in the Crohn's group and 5.9 years in the other. Similarly the mean duration of bowel symptoms at presentation was 4.2 years in the Crohn's group and 7.2 years in the other group. All the other parameters in Table 1 were similar in those with and without CD. Inflammatory markers like ESR and CRP also did not differ between the two groups (data not shown).

The clinical parameters that varied significantly by univariate analysis between those two groups were significant weight loss, fever, perianal fistula, abdominal pain, dysentery and uveitis (Table 2).

Logistic regression analysis of the most relevant clinical parameters that were significant on univariate analysis showed loss of weight as the only significant predictor for diagnosis of CD ( $P = 0.03$ , odds ratio = 28, Table 3).

Other interesting observations in this study were:

1. Two patients with CD and arthropathy had concomitant pulmonary tuberculosis (no evidence of intestinal tuberculosis).
2. Two patients with CD had psoriasis.

**Table 1: Baseline demographic characteristics of patients with suspected enteropathic arthropathy**

Parameter	Crohn's disease ( <i>n</i> = 14)	No Crohn's ( <i>n</i> = 15)	Significance
<b>Geographical origin</b> (Regions in India)	North-1 East-8 South-5 West-0	North-5 East-6 South-4 West-0	0.219
<b>Mean age (yrs)</b>	34.9	46	0.057
<b>Male: Female</b>	8:6	9:6	0.214
<b>Type of arthritis</b>	10	7	
Spondyloarthropathy (SpA)* type			
(Oligoarticular or spine alone)			
Polyarticular	2	6	0.274
Rheumatoid (RA) † type arthritis			
RA + SpA type	1	1	
‡ Monoarthritis	1	1	
<b>History of</b>			
Bleeding per rectum	7	7	
Perianal fissure	4	4	0.262
Oral ulcer	3	0	

\*Fulfilling ACR criteria of RA

†Fulfilling European spondyloarthritis study group criteria

‡Fulfilling criteria for both RA and SpA

**Table 2: Clinically significant differences between those with CD and those without CD**

Parameter	Crohn's disease (n = 14)	No Crohn's (n = 15)	Significance	Odds ratio
Significant weight loss	12	1	< 0.001	84 (5.24 < OR < 3352.21)
Presence of fever	11	0	< 0.001	Undefined
Perianal fistula	4	0	0.02	Undefined
Abdominal pain	8	2	0.013	8.67 (1.11 < OR < 85.10)
History of dysentery	4	0	0.02	Undefined
Uveitis	6	1	0.01	10.50 (0.40 < OR < 277.75)

**Table 3: Logistic regression analysis for independent clinical predictor of the diagnosis of CD**

Variable	Wald	Significance
Loss of weight <sup>§</sup>	4.3183	0.0377
Perianal fistula	0.0001	0.9933
Fever	0.0167	0.08973

<sup>§</sup> Odds ratio=28

- One patient with CD had Systemic Lupus Erythematosus (SLE) with very high anti cardiolipin antibody but without any obvious thromboembolism.

All patients with CD were treated with Sulfasalazine and Methotrexate. None of them could afford Biological agents. During the 5.54 (+/-1.71) years follow up period, dysentery, abdominal pain and fever completely resolved with treatment in all patients. Patients with perianal fistula had surgical intervention in addition to the medical therapy and there has been no recurrence of fistula till date. All patients gained weight following treatment. Although joint symptoms improved in all, four of them had recurrent arthritis requiring intra articular steroid injections. One patient with severe diffuse polyarthritis has been given a single pulse of IV Methyl Prednisolone. One of the patients had to undergo a Total Hip Replacement for advanced hip joint disease. Two patients had recurrent uveitis requiring topical and systemic steroids. The CD patient with SLE who has been on steroids developed pulmonary tuberculosis for which she was treated. Subsequently she also developed pulmonary Aspergilloma.

The non Crohn's group was also treated with Sulfasalazine with or without Methotrexate, in view of chronic inflammatory arthropathy. During the 3.27 (+/- 2.13) years follow up period of these patients, two of them had persistent bowel symptoms including recurrent bleeding per rectum, requiring blood transfusion in one. Repeat colonoscopy in both these patients revealed Ulcerative Colitis. They were given steroid pulses and enema, in addition to the existing therapy, and are currently doing well.

There was no death during the follow up period.

## Discussion

This first ever report on Crohn's arthropathy from India revealed histologically unequivocal CD in half the suspected cases (14 out of 29) and significant loss of weight was the single most independent clinical predictor with an Odds ratio of twenty eight. This clinical clue is a novel finding which would enable detection of more cases of CD in India, where the disease is under recognized.<sup>[11]</sup>

One of the difficult areas in differentiation may be that from tuberculosis of the intestine.<sup>[12,13]</sup> The absence of diffuse, confluent macro granuloma with caseation can rule out intestinal tuberculosis with reasonable precision.

Most of the common features of CD seen in our patients like young male in thirties, perianal fistula, recurrent abdominal pain, dysentery, uveitis, fever and loss of weight are described in literature.<sup>[14,15]</sup>

Significant loss of weight, an independent predictor of diagnosis in CD, as found in this study may be due to high level of tumour necrosis factor (TNF) alpha which can well explain the very basis for highly successful response to treatment with TNF antagonists in CD.

Limitations of this study include small number of patients, retrospective analysis of datasheets and a skewed population in a referral centre. However, this study can act as a sensitizer to create awareness for this condition in our country.

A large multicentric, longitudinal population based study involving subjects from all the regions of India and the Indian subcontinent with HLA delineation may bring out more information about CD associated arthropathy. Interestingly CD has been reported from southern India<sup>[11]</sup> in contrast to infective colitis, microscopic colitis and ulcerative colitis from northern India.<sup>[16,17]</sup>

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## Expert's Comments

### Gut Inflammation in Patients with Spondyloarthropathy is Prevalent and is Linked to Crohn's Disease

Spondyloarthropathies (SpA) are a related group of frequent disorders with common clinical and genetic characteristics. Ankylosing spondylitis (AS) is the prototype disease in this concept. Over recent years, evidence has accumulated that the gut mucosa is an important disease related site of inflammation in the SpA complex, and that this type of gut inflammation is immunologically strongly related to Crohn's disease (CD). Not only is CD prevalent among patients with arthropathy and chronic abdominal pain or other clinical symptoms reminiscent for inflammatory bowel disease (IBD), as outlined elsewhere in this journal issue. Silent or subclinical gut inflammation has been described in up to two-thirds of patients with SpA.<sup>[1]</sup> Different molecular features link the gut inflammation in SpA patients with classical CD.<sup>[2]</sup> These features include lymphocyte homing markers and macrophage markers. Also, immunological features like disease specific antibodies (anti-Sacharomyces cerevisiae antibodies or ASCA) may link SpA to IBD.

E-cadherin mediates intercellular adhesion in epithelial cells (not only epithelial cell–cell adhesion; also affinity with the  $\alpha E\beta 7$  integrin on intra-epithelial T cells). An upregulation of E-cadherin and its associated catenins was demonstrated in clinically overt IBD. In SpA, similarly, an increased expression of the proteins of the E-cadherin/catenin complex in subclinical gut inflammation has been described. A particular subset of macrophages expresses the scavenger receptor CD163. Functional analysis of the CD163 macrophages suggests that they could contribute to the inflammation process of chronic gut and joint inflammation, amongst others because of their capacity to produce the proinflammatory cytokine TNF $\alpha$ . In SpA, increased representation of the CD163 subset has been observed in gut mucosa as well as in synovium. The ASCA are typical serum antibodies in patients with CD. Recently, we described increased levels of ASCA (IgA isotype) in patients with AS.

What has become clear from the different studies describing immune alteration in the gut in patients with SpA, is the fact

that there is a whole immune cascade from early preclinical molecular immune changes to clinically overt CD. The genetic or environmental factors that determine the progression within this cascade are largely unknown. Indeed, over time, some patients with SpA and gut inflammation may reverse to normality, while others progress to develop overt CD.<sup>[3]</sup>

The recognition of the immune link between SpA and IBD, has given a special impetus towards the development of new therapies in SpA. Indeed, given the immunological link between the gut in SpA and IBD on the one hand and between gut and joint inflammation in SpA on the other hand, it was an attractive hypothesis to test that immunomodulators interfering with gut inflammation would also be of benefit for patients with SpA. Not only was salazopyrine first evaluated and found effective in patients with SpA. More recently, TNF antagonists like infliximab were successfully developed in AS and SpA.<sup>[4]</sup> A special scientific challenge in this respect is the fact that more TNF blockers than in the case of IBD are effective in AS. Etanercept is an example of such a drug with discordant efficacy in both diseases. The biological basis of this discrepancy is currently still under research.

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## Expert's Comments

### Diagnosing Crohn's Disease in Patients with Arthritis

The arthritis associated with Crohn's disease occurs in up to 26% of those diagnosed with the gut disorder.<sup>[1]</sup> The inflammatory peripheral arthritis classically involves the knees and ankles, affects fewer than five joints, often coincides with flares of Crohn's disease, but lasts less than 10 weeks before spontaneous improvement. A less common polyarticular arthritis similar to rheumatoid arthritis has also been described, persists long-term and remains independent of the bowel's disease activity. Finally, Crohn's patients may also develop an inflammatory spinal and sacroiliac arthritis that is indistinguishable from ankylosing spondylitis.

The connection between arthritis and Crohn's disease is often made by the appearance of joint symptoms at or after the onset of bowel symptoms. The arthritis often begins in the first years of Crohn's disease and especially in children, up to 70% of joint flares coincide with exacerbations of intestinal disease.<sup>[2]</sup> However, the diagnosis of Crohn's disease is sometimes made years after the onset of arthritis, especially in patients with a lack of abdominal symptoms and negative testing for fecal occult blood. In some cases, the treatment of arthritis with nonsteroidal anti-inflammatory drugs, sulfasalazine, or methotrexate may by itself cause gastrointestinal side effects that delay the consideration of the diagnosis of Crohn's.

The accompanying paper<sup>[3]</sup> takes the unusual approach of searching for Crohn's disease in arthritis patients, rather than for arthritis in Crohn's patients. Excluding only those arthritis patients with irritable bowel or hemorrhoids, the authors performed ileocolonoscopy with biopsy on 29 with chronic abdominal pain, diarrhea, dysentery, or perianal abscess or fistula. Only two biopsies were normal, and 14 cases of Crohn's disease were newly diagnosed. Weight loss proved to be the only significant predictor of Crohn's disease, while fever, perianal fistula, abdominal pain, history of dysentery, and uveitis were also more common in those with Crohn's. Although the series of patients is small, the rate of discovering colitis was

high, with simple items from the history and physical exam providing important clues about the presence of Crohn's. Such findings indicate that a diagnosis of Crohn's disease needs to be considered more frequently in patients with a chronic inflammatory arthritis who also develop even apparently minor bowel symptoms or nonspecific systemic findings of weight loss or fever. From the data presented, the type of arthritis (oligoarticular peripheral arthritis, polyarticular rheumatoid-like arthritis, or spondylitis) does not predict the presence of Crohn's disease. Instead, clinical vigilance and performance of colonoscopy can aid in a more rapid diagnosis.

Fortunately, there is considerable overlap in medications effective for inflammatory arthritis and Crohn's disease. Methotrexate and sulfasalazine were remarkably effective in the current study and required only occasional augmentation by corticosteroids. In those patients with an insufficient response of either the intestinal or joint disease, the use of the TNF $\alpha$  antagonists infliximab or adalimumab provides real hope for control of inflammation.<sup>[4]</sup> However, heightened awareness of the connection between arthritis and Crohn's disease is the first step towards initiating effective therapy.

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## Expert's Comments

### Crohn's Disease Associated Enteropathic Arthritis: An Often-Overlooked Entity

This is the first study of its kind from India where the prevalence of Crohn's disease (CD) among individuals presenting with enteropathic arthropathy. The authors found that 14 of the 29 patients studied had histologically confirmed CD.

Among individuals with CD there was a significantly higher frequency of individuals with weight loss, fever, perianal fistula, abdominal pain, dysentery, and uveitis. Among these factors, logistic regression analysis showed loss of weight as only





independent predictor of CD.

While there are obvious limitations in a retrospective analysis, this study brings forth several interesting issues. First, it would serve to create a greater awareness among those caring for these individuals regarding the need to perform colonoscopy among those who present with manifestations of enteropathic arthritis. Second, treatment of these individuals has involved the use of a combination of methotrexate and sulphasalazine as opposed to the latter alone for peripheral arthritis associated with other seronegative spondyloarthropathies. For the most part the dictum has been to treat peripheral arthritis in males with sulphasalazine alone if differentiation into specific syndromes is not possible. The combination is required only if one agent alone does not produce in satisfactory response.<sup>[1]</sup> Thirdly, differentiation from tuberculosis (TB) is essential not only since antitubercular therapy is indicated there, but also since anti-tumor necrosis factor, which has been used for CD, increases the probability of reactivation of TB.<sup>[2]</sup>

One issue that merits special consideration is the use of advanced statistical techniques in studies where the readers might

be interested in applying the results to individual patients. Thus, while the patients who were first seen upto August 1998 and followed for more than 6 years, the mean duration of follow up of patients with CD was 5.54 years and those without CD was 3.27 years when none of the patients dropped out in this period.

The paper should encourage other workers in this area to consider CD as a probable diagnosis among those who present with enteropathic arthropathy.

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