Research Article

STUDY OF EXTRA-INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

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A B S T R A C T

Background: There is a paucity of reports on extraintestinal manifestations (EIMs) in patients with inflammatory bowel diseases (IBD) from south India.

Methods: From November 2016 to December 2018, consecutive IBD patients, both newly diagnosed as well as already diagnosed IBD patients who were willing to consent for detailed clinical examination and investigations were enrolled in the study. The disease phenotype or severity and location were classified according to the Montréal classification. All underwent magnetic resonance imaging (MRI) of sacroiliac joints, LFT, transabdominal ultrasound, and dual energy X-ray absorptiometry (DEXA) scanning at neck femur (bilateral) and L4-L5 spine.

Results: Sixty patients were analysed, 31 had Crohn's disease (CD) and 29 had ulcerative colitis (UC). Thirty-four percent had at least one while 16 % suffered from multiple EIMs. Except for episcleritis, the frequency of individual EIMs did not differ between CD and UC patients. Twenty-two percent had peripheral arthritis, 12 % had ankylosing spondylitis, and 15 % had ophthalmological manifestations. Mucocutaneous manifestations, aphthous stomatitis, erythema nodosum and pyoderma gangrenosum (PG), were seen in 9 %. None had primary sclerosing cholangitis (PSC). More than half of patients had either osteopenia or osteoporosis on DEXA. Multivariable analysis revealed severe disease, and steroid usage were significantly associated with the presence of EIMs.

Conclusion: The prevalence of EIM is similar to that reported from west, albeit higher than that previously reported among Asian patients. Severe disease, and steroid use were associated with EIM.

INTRODUCTION

There is a paucity of reports on extraintestinal manifestations (EIMs) in patients with inflammatory bowel diseases (IBD) from south India. Extraintestinal manifestations (EIMs) seen in ulcerative colitis (UC) and Crohn's disease (CD) can be either immune mediated or occur as a result of severe intestinal inflammation or extensive resection[1].Typically, EIMs in UC and CD include arthropathies, mucocutaneous and ophthalmological manifestations, and conditions affecting the hepatobiliary system and can affect morbidity and mortality in both.The high frequency with which these four organs are involved suggests a common pathogenic link; however, the underlying mechanisms are yet not completely understood.

There are several published studies on the prevalence of EIMs in IBD patients from the West[2-4]. However, reports on the same from Asian countries are scarce[5]. Their reported frequencies range from 6 % to 47 %[6-9].

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Despite the increasing trend in the diagnosis of ulcerative colitis (UC) and Crohn's disease (CD) in India, there has been a relative paucity of data regarding the prevalence and risk factors of EIM in Indian IBD patients.Some precede the diagnosis of IBD, although the majority accompanies the underlying disease. Classic EIM in IBD includes reactive manifestations, whose course either parallel the intestinal, especially colonic, disease activity (e.g. peripheral arthritis, erythema nodosum [EN], and aphthous ulcers) or do not do so (e.g. pyoderma gangrenosum [PG], uveitis, spondyloarthropathy, and primary sclerosing cholangitis [PSC]). Another group of EIMs, like anaemia, osteopathy, cholelithiasis, nephrolithiasis, and thromboembolism, reflect IBD-related complications secondary to metabolic or anatomical, specifically small bowel abnormalities, and are seen more often in CD[10-11].Nearly one quarter of EIM affected IBD patients suffers from a combination of several EIM; it seems that the manifestation of one EIM increases the risk of developing another EIM[12].Most CD and UC patients suffering from EIMs have extensive colitis, and several of them have also a positive IBD family history.

The identification of associated risk factors may help in the early discovery of EIM in IBD patients and thereby ameliorate their treatment. Factors such as disease activity, disease location and phenotype, gender, age, smoking habit, IBD family history, NSAID use, concomitant medication, surgical history, and laboratory values are all of interest in this regard.The inflammatory bowel diseases (IBDs) are premised a consequence of genetic, environmental, and immunological interactions between host and commensal flora of the intestine. The Institute of Medical Gastroenterology at Madras Medical College in Chennai is a tertiary care centre where patients with IBD are referred to from all parts of South India. So, we decided we undertake a detailed study on prevalence and relationship of Extra-intestinal manifestations of IBD with various risk factors.

METHODS

Patients

From November 2016 to December 2018, consecutive IBD patients, both newly diagnosed as well as already diagnosed IBD patients who were willing to consent for detailed clinical examination and investigations were enrolled in the study. As Tuberculosis is endemic in our country, careful exclusion was made as described previously[13]. Patients who were HIV seropositive, having Infectious colitis, or Colon cancer were excluded.Sixty out of eighty-four(71.4%) completed full sequence of evaluation and gave their valid consent to participate in the study.

Study Design and Techniques

After taking informed consent and taking into consideration exclusion criteria, demographic, clinical, laboratory and treatment data were collected through a standard proforma. It included questions whether IBD patients experienced any Extraintestinal manifestations any time and specifically at the time of inclusion into the study. The disease phenotype/severity and location at evaluation was classified according to the Montréal classification[14], for both CD and UC patients. Severe disease was defined as either stricturing (B2) or penetrating (B3) for patients with Crohn's disease or those having endoscopic pancolitis with moderate (S2)–severe (S3) disease activity for UC[14].Peripheral arthritis was diagnosed by a trained rheumatologist and was defined as pain and swelling in one or several joints [15]. For diagnosing ankylosing spondylitis according to standard criteria [16], history of typical symptoms was taken and characteristic findings at clinical (including limited chest expansion and positive Schober's test) exam were looked for. Plain radiographic examinations of pelvis and lumbosacral spine and magnetic resonance imaging (MRI) of the both sacroiliac joints and lumbar spines were done in all patients to diagnose sacroiliitis [17]. Skin lesions like EN or PG were diagnosed clinically by a dermatologist and corroborated histopathologically by exclusion of other diagnoses when in doubt. All patients were subjected to detailed ophthalmological check-up (including slit-lamp examination) for episcleritis, scleritis, uveitis, and retinal vascular changes. To look for hepatobiliary involvement, liver function test (LFT) and transabdominal ultrasound were done in all the patients. Those demonstrating a cholestatic pattern on LFT were subjected to magnetic resonance cholangiography (MRC) for PSC.

Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DEXA) using Lunar DXA system at neck femur (bilateral) and L4-L5 spine. A T-score of −1 to −2.49 was taken as osteopenia and ≤−2.5 as osteoporosis as per WHO guidelines[18].

Statistical Analysis

Data was analysed for the whole cohort and also separately for CD and UC patients. Continuous variables were expressed as mean and standard deviation (SD), while categorical variables were expressed as percentages. Patients' baseline characteristics were compared using the Mann–Whitney U test and Pearson's chi-square test for continuous and categorical variables, respectively. Univariate analysis of various parameters between those with or without EIM was performed using the chi-square test (with Yates' correction where applicable) and the Mann– Whitney U test for categorical and continuous variables, respectively. Subsequently, the parameters found to be significant on univariate analysis for CD and UC were entered into a multivariable model (binary logistic regression) to determine the parameters associated independently with EIM. A p-value<0.05 was considered significant. Statistical analyses were done by SPSS for Windows (version 13.0, Chicago, IL).

RESULTS

A total of 60 patients (31 with Crohn's and 29 with UC) completed evaluation. The baseline demography, disease classification, and treatment details of the entire group is shown in Table 1. CD patients were more likely to have delayed diagnosis, more likely to be smokers, more likely to be malnourished and anaemic compared to UC patients. Past history of surgery and anti-tubercular therapy were exclusively seen in CD patients. Of the four patients of CD who had undergone previous surgery, three had intestinal resection (two ileal resections, one right hemicolectomy).

Table 1 Details of baseline demography, disease classification and treatment details

	Total IBD (n=60)	CD (n=31)	UC (n=29)	p-value
Male (%)	64	57	68	NS
Age at disease onset; years (mean±SD)	38.8±12.2	31.1±12.2	34.2±13	NS
Onset to diagnosis; months(range)	17(1-220)	23(1-230)	11(2-130)	P=0.017
Smoking (%)	11	18	2	P<0.05
BMI	20.7±1.9	20.3±1.7	21.2±2.0	P<0.001
Steroids (%)	42	27	57	P<0.01

Frequency of different EIMs in IBD is shown in Table 2. In all of them EIM occurred after the onset of symptoms of IBD. Except for the ocular EIMs of episcleritis, the frequency of individual EIMs did not differ between CD and UC patients.

Table 2 Frequency of different Extraintestinal manifestations

	Total IBD	CD	UC	p-value
At least one EIM present (%)	34	32	37	NS
Peripheral Arthritis (%)	22	23	21	NS
Arthritis Type 1 (%)	17	16	17	NS
Arthritis Type 2 (%)	5	6	3	NS
Ankylosing spondylitis (%)	12	13	10	NS
Back pain (%)	22	19	24	NS
Sacroiliitis on MRI	18	19	17	NS
Uveitis (%)	5	6	3	NS
Episcleritis (%)	10	3	17	P<0.001
Fatty liver (%)	17	13	21	NS
Cholelithiasis (%)	5	-	-	-
DVT (%)	3	-	-	-

Peripheral arthritis was seen in 21.7 % of IBD patients. Pauci-articular type I pattern of disease was most common. On univariate analysis, arthritis patients were more likely to have severe disease during the episode of arthritis (77 % vs. 35%; p<0.0001), had past history of surgery (19 % vs. 4 %; p= 0.02), and had increased usage of azathioprine (43 % vs. 22 %; p=0.01). Individuals with peripheral arthritis were also more likely to have concomitant EIMs like ankylosing spondylitis (55 % vs. 6 %; p<0.0001), mucocutaneous lesions (21% vs. 4 %; p<0.001), uveitis (18 % vs. 3 %; p<0.01), and either osteopenia or osteoporosis in DEXA scan (77 % vs. 40 %; p<0.001). Other variables, like age, sex, steroid use, duration of disease were not associated with arthritis.

Twenty one percent of the cohort reported back pain. More than half (62%) with back pain had sacroiliitis on MRI. Only two patients had asymptomatic sacroiliitis on MRI. Overall, 7 patients (11.7 %) had ankylosing spondylitis with not much difference between CD (n=4; 13 %) and UC (n=3; 10.3 %) groups. Of these 7 patients, one crohn's disease patient, had positive Schober's test and limited chest expansion on clinical exam with sacroiliitis on X-ray. None of them had HLA B27 positivity.

Of the ophthalmological manifestations, uveitis was seen equally in both CD and UC patients, while Episcleritis was more common in UC (17.2%) compared to CD (3.3%).

Among mucocutaneous manifestations, more patients with UC (10.3 %) than with CD (3.2%) had aphthous stomatitis (p= NS), and the overall prevalence was 6.7 %. One patient suffering from UC, had pyoderma gangrenosum (PG) in the extremities although bowel inflammation was under control. Erythema nodosum (EN) was seen in 5% of patients overall and almost equally among UC and CD.

On transabdominal ultrasound, fatty liver was detected in 16.7 % of patients in the whole IBD population. Asymptomatic cholelithiasis was found exclusively in two patients (6.5 %) of CD and one UC patient. None of the patients had any abnormal LFT or cholestasis.

One third of patients had either osteopenia or osteoporosis, almost equal between CD and UC. On univariate analysis, the two significant factors associated with the presence of osteoporosis in the IBD patients were history of previous surgery (48 % vs. 12 %; p=0.02) and presence of sacroiliitis on MRI (39 % vs. 10 %; p=0.003). Other variables, like age, gender, and steroid usage, were not associated with osteoporosis. In patients with CD, only history of previous surgery (53 % vs. 19 %; p=0.003) was associated with osteoporosis while among the patients with UC, the only significant factor associated with presence of osteoporosis was old age at the time of evaluation (41.1±14.2 vs. 32.6±12.7 years, respectively; p=0.002).

Severe disease at the time of evaluation, and ongoing steroid therapy were found to be independently and significantly associated with EIM among overall IBD patients. No association was found with family history, smoking status, disease duration, or use of immunomodulators or surgery.

When separately analysing CD and UC patients (data not shown), in patients with CD, on univariate analysis, ileocolonic location was associated with EIM (49 % vs. 19 %; p=0.001), ongoing steroid therapy (44 % vs. 9 %; p<0.001). On multivariable analysis, only ongoing steroid use (OR [95 %

CI] 5.0 [1.6–21.0]; p<0.001] was significantly associated with EIM in CD. For UC patients, univariate analysis revealed that at least one EIM was more frequently associated withextensive colitis (E3) (77% vs. 19 %; p<0.001), severe disease activity (S3) (51 % vs. 5%; p<0.01) were found to be significantly associated with EIMs in UC patients.

DISCUSSION

The important findings in this prospective cross-sectional study of South Indian IBD patients was that frequency of EIMs (involving joint, skin, oral cavity, eyes, and osteopathy) were quite high being similar to that seen in west[11], although higher than previous reports in Asian and Indian patients. One fifth of IBD patients had more than one EIM at a time. EIMs involving the bones and joints were most common. Some not so rare EIMs, like PSC, were not seen, may be because of small sample size.Severe disease were associated with EIM among overall IBD, as well as in UC and CD.

The frequency of EIM are similar to that reported in USA, and Swiss cohorts[9], while it is almost more than double of that reported from Chinese and Hong Kong cohorts[19], and similar to that reported for an UC cohort from India[20]. These differences in Asia might reflect different ethnic susceptibilities, as in multiracial communities. This is further supported by a multicentre survey of IBD in India, as well as a large single-centre cohort, which found a very high prevalence of EIMs, similar to that from the West[21-22].

As opposed to the cohorts from west[8-9], EIMs were not more common in CD than UC. This is true for the classic reactive EIMs like peripheral arthritis, ankylosing spondylitis, ocular manifestations, and aphthous ulcers. A retrospective study from China reported a higher frequency of EIM in CD compared to UC[23]. The reason for this unique finding might reflect ethnic differences or differences in screening protocol in this cohort.

In this study, an abnormal Bone mineral density was the most common EIM in both CD and UC patients. It could be explained by several factors like medications like steroids, body mass index (BMI), sex, malnutrition, intestinal resections (more so in CD), and inflammatory cytokines circulating in the body[24]. It could also reflect a high prevalence of osteoporosis in the general population, although this is less likely in healthy young, predominantly male, population. Various studies, though not all, have shown osteoporosis and osteopenia are more common in patients with IBD compared to the general population, occurring in 23 % to 59 % of patients[24].

The frequency of peripheral arthritis was similar to that reported by a Swiss study[9]. Compatible with reports from west, the peripheral arthritis was associated with increased disease severity and certain other EIMs, e.g. uveitis and aphthous stomatitis, were more frequent in these patients [8,9]. Back pain was reported by 21% and 17% had ankylosing spondylitis. Though back pain is common even in general population the high prevalence of ankylosing spondylitis in our cohort reflects the use of MRI, a very sensitive test[17], for diagnosis. A retrospective study that had used MRI to diagnose sacroiliitis in IBD patients also reported similar frequency of sacroiliitis[25].

Ophthalmological manifestations, which we specifically evaluated, seen in 13 %, is higher than reported in cohorts from west as well as from India (4 % to 8 % in UC)[19,20,22,26].

This could be a reflection of a selection bias of a more severe disease cohort as reflected by the fact that more than half of UC patients were on steroids, while almost half of the CD patients were on immune-modulators and many of the latter had undergone past resections.

The frequency of aphthous ulcers was similar to previous reports[4,9,11]. Sweet's syndrome, an EIM of CD related to disease activity, was seen in one patient. One patient with UC suffered from PG in the extremity. Erythema nodosum (EN) was seen in 5% of patients overall and almost equally among UC and CD.The prevalence of gallstones, mostly in CD patients, was comparable to other studies[27], but is similar to the prevalence of gallbladder stones in the general population of India [28]. No patient had PSC, which may be due to the low prevalence of this condition in Asian populations[22,29].

Severe disease and steroid usage were associated with EIMs reflects that disease activity is a major determinant of EIMs. Moreover, severe disease, either as steroid usage or extensive colitis in CD and UC, respectively, was predominantly associated with EIM on multivariate analysis.

The main strengths of the study are its prospective nature and meticulous search for common EIMs across multiple organs by trained physicians. Moreover, multivariable analysis was used to identify the predictors for EIM in these patients. However, referral bias couldn't be ruled out.

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