Incidence of Spondyloarthropathy in Patients with Crohn's Disease: A Population-based Study

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ABSTRACT. ***Objective.*** Spondyloarthritis (SpA) is an extraintestinal manifestation of inflammatory bowel disease with significant clinical effects, although the frequency is uncertain. We assessed the cumulative incidence and clinical spectrum of SpA in patients with Crohn's disease (CD) in a population-based cohort.

Methods. The medical records of a population-based cohort of Olmsted County, Minnesota, residents diagnosed with CD between 1970 and 2004 were reviewed. Patients were followed longitudinally until migration, death, or December 31, 2010. We used the European Spondylarthropathy Study Group, Assessment of Spondyloarthritis international Society (ASAS) criteria and modified New York criteria to identify patients with SpA. The Kaplan-Meier method was used to estimate the cumulative incidence of SpA following diagnosis of CD.

Results. The cohort included 311 patients with CD (49.8% females; median age 29.9 yrs, range 8–89). Thirty-two patients developed SpA based on ASAS criteria. The cumulative incidence of SpA after CD diagnosis was 6.7% (95% CI 2.5%–6.7%) at 10 years, 13.9% (95% CI 8.7%–18.8%) at 20 years, and 18.6% (95% CI 11.0%–25.5%) at 30 years. The 10-year cumulative incidence of ankylosing spondylitis was 0, while both the 20-year and 30-year cumulative incidences were 0.5% (95% CI 0–1.6%).

Conclusion. We have for the first time defined the actual cumulative incidence of SpA in CD using complete medical record information in a population-based cohort. The cumulative incidence of all forms of SpA increased to approximately 19% by 30 years from diagnosis of CD. Our results emphasize the importance of maintaining a high level of suspicion for SpA when following patients with CD. (First Release Sept 15 2012; J Rheumatol 2012;39:2148–52; doi:10.3899/jrheum.120321)

Key Indexing Terms:
SPONDYLOARTHRITIS
EPIDEMIOLOGY
CROHN'S DISEASE
ANKYLOSING SPONDYLITIS

Arthritis is one of the most common extraintestinal manifestations of inflammatory bowel disease (IBD), with a 10% to 35% prevalence reported in patients diagnosed with Crohn's disease (CD)[1]. IBD has been associated with both axial and peripheral arthritis. The prevalence of axial arthritis has been estimated in the literature to be 3%–25%, while peripheral arthritis occurs in about 5%–20% of patients[1,2,3].

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Supported in part by the Mayo Foundation for Medical Education and Research; and the Rochester Epidemiology Project (grant number R01 AG034676 from the National Institute on Aging).

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Accepted for publication July 4, 2012.

The peripheral arthritis associated with IBD is usually seronegative (i.e., rheumatoid factor is absent) and nonerosive; however, erosive disease that affects the hip, elbows, and metacarpophalangeal and metatarsophalangeal joints has been described in IBD[3]. Pauciarticular peripheral arthritis is strongly correlated with other extraintestinal manifestations of IBD such as erythema nodosum and uveitis, and often occurs in association with active bowel symptoms. Polyarticular peripheral arthritis is associated with uveitis but no other extraintestinal manifestations and is not as strongly associated with IBD activity[3,4,5].

Axial involvement includes sacroiliitis and spondylitis. The ankylosing spondylitis (AS) of CD is mainly asymmetric, in contrast to idiopathic AS[6,7,8,9].

The frequency with which spondyloarthritis (SpA) occurs in patients with CD is not well studied. A population-based report from Norway concluded that the prevalence of AS is 3.7% in patients seen 6 years after diagnosis of IBD[10]. This study also described the occurrence of psoriatic arthritis, reactive arthritis, and undifferentiated SpA in IBD to be 0.8%, 0.5%, and 17%, respectively[10]. AS occurred significantly more often in patients with IBD than in the general

population, and was more common in men. HLA-B27, peripheral arthritis, enthesitis, and uveitis were significantly more common in patients with IBD who have associated AS compared to patients with IBD who did not have AS[10].

To date, no population-based cohort study that describes the incidence of SpA in patients with IBD has been published. We examined both the cumulative incidence and the clinical features of SpA in a population-based US cohort of patients with CD.

MATERIALS AND METHODS

The Rochester Epidemiology Project (REP) is a unique medical records linkage system developed in the 1950s and supported by the National Institutes of Health. It exploits the fact that virtually all healthcare for the residents of Olmsted County is provided by 2 organizations: Mayo Medical Center, consisting of Mayo Clinic and its 2 affiliated hospitals (Rochester Methodist and Saint Marys), and Olmsted Medical Center, consisting of a smaller multispecialty clinic and its affiliated hospital (Olmsted Community Hospital). In any 3-year period, over 90% of county residents are examined at either of the 2 healthcare systems[11]. Diagnoses generated from all outpatient visits, emergency room visits, hospitalizations, nursing home visits, surgical procedures, autopsy examinations, and death certificates are recorded in a central diagnostic index. Thus, it is possible to identify all diagnosed cases of a given disease for which patients sought medical attention.

The resources of the REP were used to identify a population-based cohort of patients diagnosed with CD from 1970 through 2004[12,13,14]. All cases of CD were diagnosed based on a consistent definition — cases had to meet at least 2 of the following criteria: (1) clinical history of abdominal pain, diarrhea, weight loss, malaise, and/or rectal bleeding; (2) endoscopic findings of mucosal cobblestoning, linear ulceration, skip areas, or perianal disease; (3) radiological findings of strictures, fistula, mucosal cobblestoning, or ulceration; (4) macroscopic appearance of bowel wall induration, mesenteric lymphadenopathy, and "creeping fat" at laparotomy; or (5) pathological findings of transmural inflammation and/or epithelioid granulomas[12].

Lifetime data on musculoskeletal symptoms and disease were recorded retrospectively, and the patients were followed longitudinally until moving from Olmsted County, death, or December 31, 2010. Approval for the study was obtained from the institutional review boards of Mayo Clinic and Olmsted Medical Center.

The European Spondylarthropathy Study Group (ESSG) criteria, modified New York criteria, and Assessment of Spondyloarthritis international Society (ASAS) criteria were applied retrospectively in identifying patients with SpA[7,8,9,15]. Demographic data including sex, date of birth, and date of diagnosis of CD were recorded as described[12,13,14], as well as anatomic location of CD, date of arthropathy diagnosis by the treating physician, diagnosis of another primary inflammatory arthritis, family history of arthropathy, and characteristics of SpA. These included presence of inflammatory back pain, synovitis, psoriasis, nongonococcal urethritis/cervicitis, alternating buttock pain, enthesitis, sacroiliitis (based on radiographs or magnetic resonance imaging), which was diagnosed both clinically and radiographically, uveitis, limitation in spine motion, lumbar spine pain, limitation of chest expansion, radiographic evidence of ankylosis, HLA-B27 status, oligoarthritis and specific joints involved, or polyarthritis and specific joints involved; this information was recorded based on physician diagnosis in the medical record. The abstracted data included diagnoses of SpA or its clinical features seen in usual practice by treating physicians, most often a primary care physician or rheumatologist. Diagnoses of uveitis and psoriasis were made by an ophthalmologist or dermatologist, respectively.

Diagnosis of specific forms of SpA included those based on treating physician diagnosis. All patients who had either inflammatory back pain or synovitis were included in our study as having SpA based on the ESSG criteria because all of these patients already carried a diagnosis of IBD[7,8,9,15]. Patients were also included as having AS if there was evidence of either limitation in spine motion and lumbar spine pain in the setting of radiographic evidence of ankylosis based on the modified New York criteria for this disease[15]. Finally, all patients who had arthritis, enthesitis, or dactylitis were included in our study as having SpA based on the ASAS criteria because all of these patients already carried a diagnosis of CD[8,9].

In addition to including treating physician diagnoses of SpA, we searched individual medical records for features of this disease even when a formal diagnosis was not made; those with features of SpA that correlated with the ESSG and ASAS criteria were included as having this diagnosis. All records were abstracted by RS with independent abstraction and confirmation of the features of SpA by ELM.

The cumulative incidence of SpA after CD diagnosis was estimated using the Kaplan-Meier method. Ninety-five percent CI for the observed proportions (%) were based on the exact binomial distribution. Also calculated were the prevalence of psoriasis, nongonococcal urethritis/cervicitis, alternating buttock pain, enthesitis, sacroiliitis, uveitis, plantar fasciitis, Achilles tendonitis, oligoarthritis, and polyarthritis.

RESULTS

Incidence. A total of 311 patients with CD were identified, of whom 49.8% were women, and the median age at diagnosis of CD was 29.9 years (range 8–89 yrs; Table 1). Prior to CD diagnosis, based on the ESSG criteria, the prevalence of SpA was 1.3% (95% CI 0.4%–3.3%), with 4 patients from the total of 311 patients with CD who had been diagnosed with SpA prior to the diagnosis of CD. No patient carried a diagnosis of AS. Based on the ASAS criteria, 13 patients from the total of 311 with CD had been diagnosed with SpA prior to a diagnosis of CD; therefore, the prevalence of SpA based on ASAS criteria prior to CD diagnosis was 4.2% (95% CI 2.2%–7.0%). The median number of years from time of SpA diagnosis to CD diagnosis in these patients was 5.5 years (range 0.2–43.5 yrs). The patients diagnosed with SpA prior to CD diagnosis were excluded from analysis of incidence of arthritis subsequent to diagnosis of CD.

Following the incident date of CD diagnosis, 14 of 307 patients were diagnosed with SpA according to the ESSG criteria. The cumulative incidence of a diagnosis of SpA after an established diagnosis of CD was 2.6% (95% CI 0.7%–4.5%)

Table 1. Baseline characteristics of 311 patients with Crohn's disease in the Olmsted County population-based cohort (1970–2004).

Characteristic	N (%)
Male	156 (50.2)
Female	155 (49.8)
Age at diagnosis, yrs	
< 18	43 (13.8)
18–40	163 (52.4)
> 40	105 (33.8)
Disease location	
Small bowel	101 (32.5)
Ileocolitis	104 (33.7)
Colitis	106 (34.1)

at 10 years, 6.1% (95% CI 2.4%–9.7%) at 20 years, and 9.8% (95% CI 3.2%–15.8%) at 30 years (Figure 1).

According to the ASAS criteria, 32 of 298 patients were diagnosed with SpA following a diagnosis of CD. The cumulative incidence of a diagnosis of SpA after an established diagnosis of CD was 6.7% (95% CI 3.5%–9.7%) at 10 years, 13.9% (95% CI 8.7%–18.8%) at 20 years, and 18.6% (95% CI 11%–25.5%) at 30 years (Figure 2). The median number of years from time of CD diagnosis to SpA diagnosis in these patients was 9.9 years (range 0.4–32.0 yrs).

In our cohort, a total of 18 patients were diagnosed with SpA and 2 were specifically diagnosed with AS based on the ESSG criteria in the pre- and post-CD diagnosis periods. Fourteen out of 18 patients who carried a diagnosis of SpA were female; in the AS group, 1 of 2 patients was female. The majority of patients diagnosed with either SpA or AS had associated Crohn's ileocolitis or colitis rather than ileitis. In those diagnosed with SpA, 11% of patients (2 out of 18) also showed Crohn's ileitis, 50% (9 out of 18) had ileocolitis, and 39% (7 out of 18) had colitis. Finally, in patients diagnosed with AS, none had Crohn's ileitis, while 1 patient had ileocolitis and 1 had colitis.

A total of 45 patients were diagnosed with SpA based on ASAS criteria in the pre- and post-CD diagnosis periods. Thirty out of these 45 patients were female. The majority of these patients had Crohn's ileocolitis or colitis rather than ileitis. Specifically, Crohn's ileitis, ileocolitis, and colitis were present in 18% (8 out of 45), 33% (15 out of 45), and 49% (22 out of 45), respectively.

Subtypes. AS was diagnosed in 2 of 311 patients after diagnosis of CD. The 10-year cumulative incidence of AS was 0, while both the 20-year and 30-year cumulative incidences were 0.5% (95% CI 0–1.6%). There were no physician diagnoses of reactive, psoriatic, or undifferentiated SpA in our cohort.

Clinical characteristics. Clinical features of the SpA in the total cohort of 311 patients are shown in Table 2.

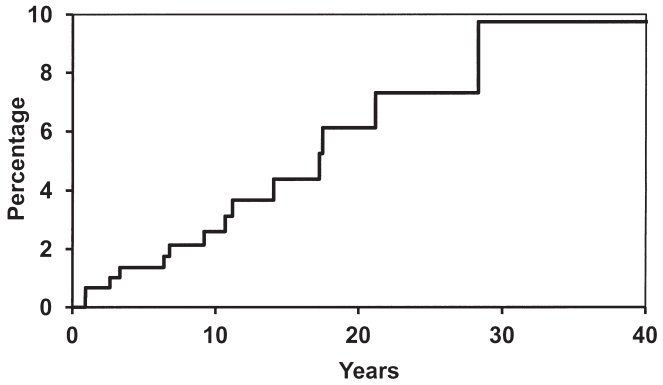

Figure 1. Cumulative incidence (1 minus survival-free) of any spondyloarthritis (based on European Spondylarthropathy Study Group criteria) from diagnosis of Crohn's disease among 307 Olmsted County, Minnesota, residents with Crohn's disease (1970-2004).

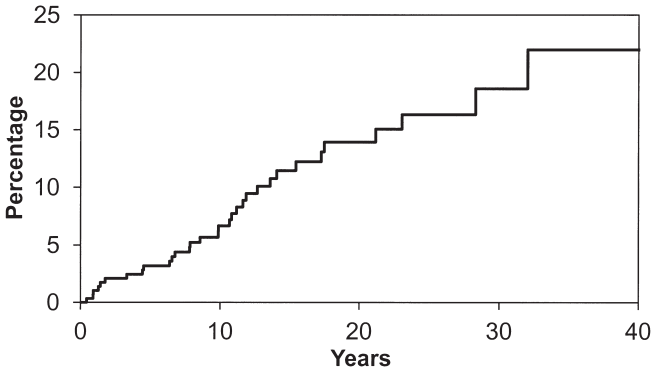

Figure 2. Cumulative incidence (1 minus survival-free) of any spondyloarthritis (based on Assessment of Spondyloarthritis international Society classification criteria) from diagnosis of Crohn's disease among 298 Olmsted County, Minnesota, residents with Crohn's disease (1970-2004).

DISCUSSION

The major aim of our study was to define the incidence and clinical features of SpA in patients with CD. To our knowledge, our study is the first to define the actual cumulative incidence of SpA in a population-based cohort of CD using complete medical record information. Specifically, the cumulative incidence of any SpA increased to about 1 in 10 patients by 30 years from CD diagnosis based on the ESSG criteria, and about 1 in 5 patients by 30 years after CD diagnosis according to the ASAS criteria.

The occurrence of clinical features of SpA became more frequent following the diagnosis of CD. Notably, there were no diagnoses of sacroiliitis prior to diagnosis of CD; however, the incidence of this diagnosis increased to 1.6% following the diagnosis of CD. Also, the incidences of buttock pain, plantar fasciitis, uveitis, oligoarthritis, and polyarthritis more than doubled following the diagnosis of CD. The

Table 2. Clinical characteristics of spondyloarthritis (SpA) in 311 patients with Crohn's disease (CD) from a population-based cohort of Olmsted County residents.

SpA Feature	Features Present Prior to CD, n	Features Appearing After CD, n
Psoriasis	5	9
Urethritis/cervicitis	1	0
Buttock pain	1	6
Plantar fasciitis	4	12
Achilles tendonitis	4	4
Sacroiliitis	0	5
Uveitis	2	10
Oligoarthritis	3	9
Polyarthritis	3	7
Inflammatory back pain (see Discussion)	0	2

most common feature prior to a diagnosis of CD was psoriasis, while the most common feature following the diagnosis of CD was plantar fasciitis. The HLA-B27 status among patients with SpA would be interesting, but this was not systematically assessed in our patients because this was not a routine laboratory study.

Our results are in contrast to those from Bernstein and colleagues, who reported that uveitis/iritis was the most common extraintestinal manifestation in CD[2]. However, that was a prevalence study that abstracted 5 diagnoses using *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes: primary sclerosing cholangitis, AS, uveitis/iritis, pyoderma gangrenosum, and erythema nodosum. In contrast, we studied the cumulative incidence of these conditions, and diagnoses were based on data abstracted from the actual medical record.

A cross-sectional population-based study from Norway of the prevalence of SpA and associated clinical characteristics in 406 patients with CD and 6-year physician followup revealed the prevalence of AS to be 6.0% and that of SpA was 26%[10]. The occurrence of enthesitis, uveitis, and peripheral arthritis was more common in those who met criteria to be diagnosed with AS rather than those diagnosed with just inflammatory back pain or sacroiliitis.

Several other studies have described the prevalence of articular manifestations and SpA in CD[16,17,18,19]. In particular, the investigation by Salvarani, *et al* was a cross-sectional study from Italy and The Netherlands, whereas ours is a true population-based cohort. In contrast to these previous studies, our work was an incidence study with up to 30-year followup after diagnosis of CD. Although the number of patients in our study is smaller, it has the advantages of identifying features of SpA from chart-based data abstraction of physician diagnoses and a large number of person-years of followup along with information about the presence of features of SpA prior to the diagnosis of CD.

Patients in our study diagnosed with SpA were more likely to have either Crohn's ileocolitis or colitis compared to Crohn's ileitis based on both ESSG and ASAS criteria. This finding is in agreement with Greenstein, *et al*, who reported that extraintestinal manifestations of ulcerative colitis or CD were more likely to be associated with colonic disease (42%) when compared to small bowel disease[20]. Increased gut permeability has been discussed in the setting of IBD and perhaps this phenomenon is more often seen in the colon[6]. Higher permeability of the colon at sites affected by CD could lead to translocation of activated T cells to joints and thereby cause inflammation. The pathobiology of the association of IBD and SpA remains to be fully elucidated.

The cumulative incidence of SpA was higher using the ASAS criteria. Unlike the ESSG criteria, the ASAS criteria use (but do not require) magnetic resonance imaging (MRI) in addition to radiographic data to diagnose sacroiliitis; MRI is more sensitive for sacroiliac inflammation. Also, a diagnosis of peripheral SpA based on ASAS criteria requires a diagnosis of arthritis, dactylitis, or enthesitis, plus a feature of SpA, which includes CD[21]. Because more patients in our cohort were diagnosed with arthritis or enthesitis rather than inflammatory back pain or pure synovitis (as required by ESSG criteria), the incidence of any SpA was higher when the ASAS criteria were applied.

Our study included only patients who came to clinical attention for extraintestinal SpA-related symptoms. Systematic screening of all patients with CD, for example by radiographic imaging of the sacroiliac joints, was not performed. A further limitation is that not all patients were screened for features of spondyloarthropathy by a rheumatologist, which may have limited ascertainment of possible SpA disease features. Additionally, a diagnostic approach to patients with CD to assess for SpA and its features with use of classification criteria was likely not undertaken because most patients were seen by a primary care physician; likely there were fewer diagnoses seen in our cohort because of difficulty making this diagnosis without evaluation by a rheumatologist. The ESSG classification criteria call for a diagnosis of inflammatory back pain, which is a difficult diagnosis to make. As evidenced in our study as well as others, information about inflammatory back pain is very often either not systematically interrogated or not recorded in a way that permits recovery in retrospective medical record review, and likely was underdiagnosed[7,8,9]. However, this was a population-based study of patients seen in usual clinical practice, in which not all patients undergo subspecialty evaluation. Hence, our estimates based on ASAS and ESSG criteria might be regarded as the minimum estimate of incidence and frequency of disease features. Finally, a limitation in using the ESSG criteria in classifying SpA is its low sensitivity and specificity in mild and early cases.

AS is perhaps the best defined of the spondyloarthritides, and likely the diagnosis that is best recognized in the community. There were no diagnoses of reactive, undifferentiated, or psoriatic spondyloarthritides found in the medical records. We could not reliably evaluate the diagnostic criteria for these subtypes of SpA in our analysis.

Our study shows that the features of SpA were most commonly diagnosed within the first 10 years of diagnosis of CD and the frequency of diagnosed SpA increased from time of diagnosis of CD. Additional studies are necessary to better define the immunobiology of SpA in patients with IBD.

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R. Shivashankar, E.V. Loftus Jr, W.J. Tremaine, T. Bongartz, W.S. Harmsen, A.R. Zinsmeister, E.L. Matteson. Incidence of spondyloarthropathy in patients with Crohn's disease: A population-based study. J Rheumatol 2012;39:2148-52. Table 2 should appear as follows. We regret the error.

doi:10.3899/jrheum.120321.C1

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Digital Gangrene in a Patient with Systemic Lupus Erythematosus and Systemic Sclerosis

Omair MA, Bookman A, Mittoo S. Digital gangrene in a patient with systemic lupus erythematosus and systemic sclerosis. J Rheumatol 2012;39:1895-7. Degrees for the first author should be given as Mohammed A. Omair, MBBS, SF Rheum. We regret the error.

doi:10.3899/jrheum.120123.C1