# Crohn's Disease Behavior and Location is Altered when Associated with Primary Sclerosing Cholangitis

Oren Iny MD, Henit Yanai MD, Shay Matalon MD, Erwin Santo MD, Oren Shibolet MD, Iris Dotan MD* and Nitsan Maharshak MD*

Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

**ABSTRACT:** **Background:** Up to 3.4% of Crohn's disease (CD) patients will be diagnosed with concomitant primary sclerosing cholangitis (PSC). Despite the worldwide increase incidence of CD, data on the clinical characteristics of PSC-CD patients are scarce.

**Objectives:** To clinically characterize CD in patients who have concomitant PSC.

**Methods:** A retrospective case-control analysis was conducted with 18 CD patients with concomitant PSC who attended the Inflammatory Bowel Disease Center at the Tel Aviv Sourasky Medical Center between 2011–2014 (PSC-CD patients). They were matched by age, gender, and disease duration to 90 control patients (those with CD who did not have concomitant PSC). Disease phenotype (according to the Montreal classification), demographics, and clinical data were compared in the two groups.

**Results:** PSC-CD patients were characterized by a disease that was more frequently limited to the colon (L2) (50% vs. 16%, $P = 0.004$) and by a non-stricturing and non-penetrating inflammatory phenotype (83% vs. 33%, $P = 0.0001$) compared to controls who had an increased prevalence of the penetrating phenotype (B3) (6% vs. 33%, $P < 0.05$). Use of 5-aminosalicylic acid agents as a single therapy was significantly more prevalent among PSC-CD patients than in controls (39% vs. 7%, $P < 0.005$). In contrast, biologic therapy was significantly less common among PSC-CD patients compared to controls (17% vs. 52%, $P = 0.0086$).

**Conclusions:** Patients with PSC-CD are clinically distinct from patients with isolated CD, and are characterized by predominant colonic involvement and an inflammatory, non-stricturing and non-penetrating phenotype.

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**KEY WORDS:** Crohn's disease, primary sclerosing cholangitis (PSC), Montreal classification, inflammatory bowel diseases (IBD)

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disorder characterized by inflammation, obliteration, and fibrosis of both the intrahepatic and extrahepatic bile ducts. The pathogenesis of PSC is not fully elucidated, but may result from impairment of immunological and non-immunological host defenses as well as from alterations in composition of enteric microbiota (dysbiosis) [1]. The continuous epithelia between the gut and the biliary tree, as well as exposure of the liver to gut-delivered antigens arriving through the portal circulation [1], are a few of the pathogenic pathways that are thought to explain the association between PSC and inflammatory bowel diseases (IBD).

PSC more prevalent in males and is often characterized by concomitant IBD. The mean age of diagnosis is 40 years [2,3]. Ulcerative colitis (UC) is diagnosed in about 65% and Crohn's disease (CD) in about 10% of PSC patients. Similarly, PSC is diagnosed in up to 7.5% of UC patients and in up to 3.4% of patients with CD [2,4,5].

Disease in UC patients who are diagnosed with concomitant PSC is clinically distinct from isolated UC. They tend to have milder intestinal symptoms and a prolonged subclinical course [2,5,6], a higher prevalence of pancolitis (87% vs. 54%), rectal sparing (52% vs. 6%), and "backwash ileitis" (51% vs. 7%) [2,4,5].

Data on clinical characteristics of patients with PSC-CD are scarce. It has been suggested that similar to UC patients, CD patients with PSC have extensive colonic involvement, and less often small bowel limited disease [2,4], leading in many cases to a diagnosis of indeterminate colitis [5,7].

Clinical characterization of PSC-CD patients is important for prediction of clinical outcome, tailoring therapy and for better understanding of disease pathogenesis. Thus, our aim in the current study was to characterize the clinical phenotype and disease location of CD patients with concomitant PSC (PSC-CD).

## PATIENTS AND METHODS

### STUDY DESIGN

A retrospective case-control study was performed, which included all patients with PSC with an established concomitant diagnosis of CD [8] who attended the Inflammatory Bowel Disease (IBD) Center at the Tel Aviv Sourasky Medical Center, a tertiary referral center, between the years 2011–2014. Each PSC-CD patient was matched to five patients with isolated CD (controls). All PSC patients were previously included in a prior study that evaluated PSC disease course [8]. All clinical data

*These authors contributed equally to this manuscript

was extracted from a digital research database of patient files maintained in the IBD Center [8]. The study was approved by the institutional review board of the Tel Aviv Medical Center.

### DEFINITIONS

CD diagnosis was defined by the treating physicians based on clinical, laboratory, endoscopic, histologic, and imaging studies. All patients had at least one endoscopic examination during the study period, except for one case. In this case colonoscopy data was not available, but a magnetic resonance enterography demonstrated strictures and dilatations of the small bowel and a right colon involvement. IBD was classified according to the Montreal classification [9].

PSC was defined as a persistent increase in cholestatic biochemistry profile, together with typical radiographic or histologic findings of PSC (intra- and/or extra-hepatic bile duct changes including segmental dilatations and structuring) [10]. Secondary sclerosing cholangitis was excluded in all cases.

The extent of colitis was defined as the most proximal involvement of inflammatory disease based on endoscopy or imaging at any time during the study period. Disease duration was determined as time elapsed since diagnosis to the last follow-up visit. Treatment was defined as documented in the most recent follow-up visit.

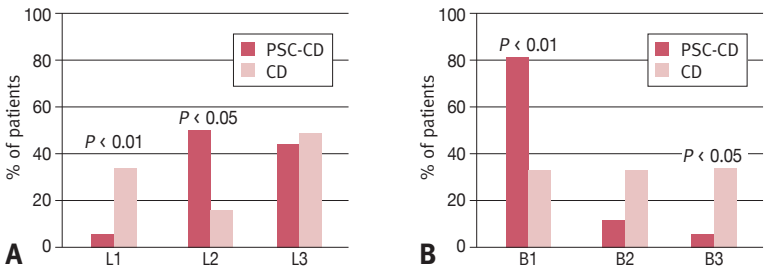
**Table 1.** Demographic characteristics of participants

| | PSC-CD N=18 | CD only N=90 | *P* value |
|---|---|---|---|
| Males, n (%) | 10 (55%) | 53 (58%) | NS |
| **Age at diagnosis**<br>CD (years)<br>PSC (years) | <br>28.4 ± 12.24<br>34.5 ± 10.6 | 26 ± 10.58 | NS |
| **Duration of disease**<br>CD (years)<br>PSC (years) | <br>11.72 ± 8.01<br>6.3 ± 3.72 | 14.17 ± 7.25 | NS |

Data are represented as mean ± standard deviation (SD)

CD = Crohn's disease, PSC = primary sclerosing cholangitis, NS = not significantly different

**Figure 1.** CD location and phenotype. **[A]** CD was more commonly located in the colon (L2) in PSC-CD patients and less commonly in the small intestine (L1) compared to controls (CD patients without PSC) according to the Vienna classification 25. **[B]** In PSC-CD patients, disease behavior was mostly categorized as non-stricturing and non-penetrating (B1) and significantly less common as penetrating disease (B3) compared to patients with isolated CD




PSC = primary sclerosing cholangitis, CD = Crohn's disease

Disease location: L1 = small intestine, L2 = colon, L3 = ileocolon

Disease behavior: B1 = non-stricturing and non-penetrating, B2 = stricturing, B3 = penetrating

### STUDY POPULATION

Patients were included if they had a diagnosis of CD and concomitant PSC based on accepted clinical, endoscopic, histologic, or imaging studies; and no history of other liver diseases or a previous liver transplant. Patients who did not fulfill the criteria of diagnosis or for whom relevant clinical information was missing were excluded from analysis. Additional data extracted from the files included medical treatment, disease duration, disease location, disease behavior, laboratory data, endoscopy results, and imaging studies as well as data regarding PSC.

The control group was selected from a total of 723 CD patients without concomitant PSC who were evaluated at the IBD Center between the years 2011–2014. Demographic data such as age at diagnosis, gender, disease duration, and smoking history were extracted from a digital research database. Controls were matched to cases for gender, age at diagnosis (± 5 years), and disease duration (± 5 years) at a ratio of 5:1.

Disease phenotype (according to the Montreal classification) and demographic and clinical data were compared between the two groups.

### STATISTICAL ANALYSIS

Data were analyzed using GraphPad Prism version 6 (GraphPad Software, Inc., California, USA). Continuous variables were analyzed using a 2-sided *t*-test and the non-parametric Mann–Whitney test, as appropriate. The chi-square test was used to explore categorical variables. All tests were 2-tailed, and the threshold for statistical significance was defined as a $P$ value < 0.05.

A biomedical statistics expert performed statistical reviews for all data (see acknowledgements).

## RESULTS

Eighteen patients (10 males) with PSC-CD were identified during 2011–2014. Their mean age at diagnosis was 28.4 ± 12.24 years, and mean CD duration was 11.7 ± 8.01 years. These patients were matched to 90 patients with isolated CD. Demographic data of patients and controls are presented in Table 1.

### DISEASE LOCATION

CD involved the colon (L2 or L3) in 17 (94%) of PSC-CD and in 59 (65%) patients of the control group ($P < 0.05$), while disease was limited to the colon (L2) in 9 (50%) of PSC-CD patients, but in only 14 (16%) of the controls ($P < 0.005$). Limited small bowel disease (L1) was noticed in only one PSC-CD patient (6%) as opposed to 31 (34%) of the control group ($P < 0.05$) [Figure 1A].

### DISEASE PHENOTYPE

The inflammatory (non-stricturing and non-penetrating) phenotype B1, was prevalent in 15 (83%) of PSC-CD patients, of which one had perianal involvement (B1p), and in 30 (33%) of the control group ($P < 0.0005$) at the time of recruitment to the study. A stricturing phenotype was found in two of the PSC-CD patients (11%) versus 30 (33%) of the controls ($P = 0.088$), while a penetrating phenotype (B3) was documented in one patient with PSC-CD (6%), who also had a perianal involvement (B3p), and in 30 patients (33%) of the control group ($P < 0.05$) [Figure 1B].

### SEROLOGY

Serologic markers have been associated with disease phenotype and progression [11-13]. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) are typically found in CD patients. This serologic marker was available for ten PSC-CD patients and was positive in only four (40%) of them: three patients (75%) with an ileocolonic disease (L2) and only one of five patients (20%) with a disease limited to the colon (L2) [Table 2]. Perinuclear antineutrophil cytoplasmic (pANCA), which is characteristic of UC, was positive in one of 14 tested patients (7%). This patient was also seropositive for ASCA and had a limited colonic disease (L2).

### TREATMENT

For UC, 5-aminosalicylic acid (5-ASA) medications are typically prescribed. However, most PSC-CD patients were treated with 5-ASA medications at a significantly higher proportion compared to the control group (66% vs. 39%, respectively, $P = 0.04$). Interestingly, 7 (39%) of the PSC-CD patients were treated with 5-ASA as a mono-therapy compared to only 6 patients (7%) of the control group ($P < 0.005$) [Figure 2]. In contrast, biologic therapy was significantly less common among PSC-CD patients compared to controls (17% vs. 52%, $P = 0.0086$), but use of immunomodulators and corticosteroids was similar among both groups [Table 2].

**Table 2.** Clinical characterization of CD with PSC patients compared to CD patients without PSC

| | PSC-CD N=18 | CD only N=90 | *P* value |
|---|---|---|---|
| **Therapy** | | | |
| 5-ASA monotherapy | 7 (39%) | 35 (39%) | 0.001 |
| 5-ASA total | 12 (66%) | 16 (18%) | 0.0371 |
| Corticosteroids | 4 (22%) | 51 (57%) | 0.74 |
| AZA/6-MP | 6 (33%) | 47 (52%) | 0.12 |
| Biologic | 3 (17%) | 3 (3%) | 0.0086 |
| Methotrexate | | 3 (3%) | |
| No treatment | | 3 (3%) | |
| **Disease location** | | | |
| Ileum only (L1) | 1 (6%) | 31 (34%) | 0.02 |
| Colon only (L2) | 9 (50%) | 14 (16%) | 0.0029 |
| Ileal and colon involvement (L3) | 8 (44%) | 45 (49%) | 0.799 |
| **Disease behavior** | | | |
| Non-penetrating and non-stenosing | 15 (83%) | 30 (33%) | 0.0001 |
| Fibrostenotic | 2 (11%) | 30 (33%) | 0.088 |
| Penetrating | 1 (6%) | 30 (33%) | 0.02 |
| **Serology** | | | |
| ASCA positive | 4/10 (40%) | | |
| Disease location | | | |
| L1 | 0/1 (0%) | | |
| L2 | 1/5(20%) | | |
| L3 | 3/4(75%) | | |
| pANCA positive | 1/14 (7%) | | |

CD = Crohn's disease, PSC = primary sclerosing cholangitis, ASCA = anti-Saccharomyces cerevisiae antibodies, pANCA = perinuclear antineutrophil cytoplasmic, 5-ASA = 5-aminosalicylic acid, AZA/6-MP = azathioprine/6-mercaptopurine

## DISCUSSION

PSC is less common among those with CD compared to UC, but its prevalence is significant and continuously increasing [14]. PSC-UC patients have been extensively studied and are characterized by a milder disease phenotype and an increased risk for colon carcinoma [15,16] compared to UC patients without PSC. The clinical approach toward these patients includes closer follow-up and surveillance. However, it is currently unknown whether PSC-CD patients differ clinically from CD patients without PSC. In this study, we have characterized the clinical phenotype and disease location of CD patients with concomitant PSC, compared to highly matched isolated CD patients. Our findings indicate a distinct disease phenotype and location in the PSC-CD patients compared to controls.

PSC-CD patients were characterized by a non-stricturing and non-penetrating (B1) disease phenotype (83% vs. 33%, $P < 0.0005$) and less often from a penetrating (6% vs. 33%, $P < 0.05$) or from a fibrostenotic disease, which was less frequent numerically but did not reach statistical significance (11% vs. 33%, $P = 0.088$) [Figure 1B], compared to the matched control group. Given the long disease duration (mean 14.4 ± 7.5 years) in these patients, these results are surprising and indicate that intestinal disease progression in PSC-CD patients is slower and less aggressive than expected as indicated by the rates of disease phenotype in the control group and in previous studies. Typically, CD progresses over time from a non-stricturing and non-penetrating inflammatory phenotype, commonly seen at diagnosis, to a fibrostenotic or penetrating phenotype. Penetrating disease had a prevalence of 35.4–40% after 5 years of

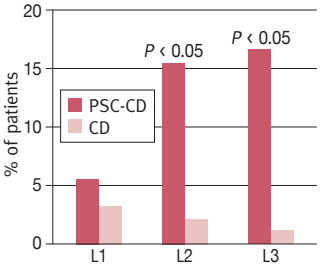



**Figure 2.** Percentage of patients treated with 5-aminosalicylic acid (5-ASA) as a monotherapy according to disease location. PSC-CD patients with disease located in the ileum (L1) or the colon (L2) were more commonly treated with 5-ASA monotherapy compared to patients with isolated CD

PSC = primary sclerosing cholangitis, CD = Crohn's disease

disease, and of 58.2–70% after 20 years of disease as described by Lovasz and co-authors [17] and by Cosnes and colleagues [18]. Similarly, stricturing (B2) phenotype was found in 32.2% of CD patients after 10 years of follow-up as described by Louis et al. [19], and in 35.4% to 58.2% after 5 and 20 years, respectively, in the study by Lovasz and co-authors [17]. In contrast, a third study focusing on CD patients demonstrated a decreased rate of stricturing disease in 18% of CD patients at 20 years from diagnosis [18].

These findings emphasize the possibility that patients with PSC-CD may have a unique non-stricturing and non-penetrating (B1) phenotype that less frequently progresses to a penetrating phenotype, and perhaps also toward a fibrostenotic phenotype, compared to CD patients who are PSC free.

Disease location in PSC-CD patients was also not typical. It rarely involved the small intestine (6% vs. 34%, respectively, $P < 0.05$) and was mainly isolated to the colon in 50% of PSC-CD patients compared to 16% in controls ($P < 0.005$) [Figure 1A]. Rates of intestinal involvement in the control group were in concordance with previous reports, where patients with a 10 year disease duration had a disease limited to the colon in 23.3% and disease limited to the small intestine in 43.3% of patients [19]. The significant colonic involvement among PSC-CD patients (94% of patients) may imply that the pathogenesis of CD in PSC-CD varies from that of isolated CD and is more similar to that of UC. Given that IBD usually precedes PSC, colonic inflammation may be associated with increased risk for liver involvement through various mechanisms (such as immunologic or microbial) in predisposed (i.e., genetic) individuals and hence, this disease is more common in UC patients [20] and in CD patients with colonic involvement.

Treatment regimens in PSC-CD patients were similar to those used in UC patients and were characterized by a high percentage of patients being treated solely by 5-ASA derivatives compared to the control group (39% vs. 7%, respectively, $P < 0.005$) [Figure 2]. These regimens probably related to the increased colonic involvement in PSC-CD patients and may have suggested that 5-ASA as monotherapy is a sufficient therapy in these patients, given the lower percentage of progression to a more severe disease phenotype (such as penetrating or fibrostenotic disease) and the low percentage of PSC-CD patients receiving biologic therapy in comparison to controls (17% vs. 52%, respectively, $P < 0.001$).

Other noted characteristics of PSC-CD patients included a slightly increased prevalence among males (55%) and a CD that preceded PSC. Our results are in agreement with previously reported data that showed that CD precedes PSC diagnosis by an average of 9 years as well as slightly higher prevalence of PSC-CD among males (60%) [21-23].

In PSC-CD patients, the apparent male predominance is in contrast to reports of a slight female predominance in patients with isolated CD [18]. The findings may indicate that hormonal factors may play a role in disease expression in our group. Furthermore, among the subgroup of patients with a non-stricturing and non-penetrating inflammatory phenotype, females have an even higher prevalence [18]. Taken together, these data further support a unique phenotype of male gender, colonic non-stricturing and non-penetrating disease among PSC-CD patients.

Our study has several limitations. It is retrospective and suffers from inherent problems of this study type. Assessment of disease location and phenotype was based on follow-up detailed in patient files; therefore, some patients were excluded due to lack of needed information. Nevertheless, most patients had recent endocsopic and small intestinal imaging studies available in the files. In addition, due to the similarities between the disease in PSC-CD and UC patients, it can be argued that our cohort was "contaminated" by UC patients. However, the patients in this cohort were well-characterized and patients who were categorized with intermediate colitis were excluded. In addition, the low prevalence of pANCA-positive serology (only one patient), suggests that misdiagnosis of UC patients as CD patients was unlikely and that the PSC-CD subgroup of patients has a unique and different characteristics compared to UC [11].

Therefore, although the number of cases is relatively small, given the paucity of data concerning PSC-CD patients, this is one of the largest studies on this population and our findings were in line with former studies. In addition, we attempted to compensate for the small number of cases through meticulous matching of each patient to five CD controls.

While the prevalence of CRC in colonic CD remains an open question, several studies suggested that the risk is similar [15,16,24]. Our study demonstrates similarities between PSC-CD and UC, supporting this potential, although among our PSC-CD patients, none were diagnosed with a CRC or adenoma. Our results suggest that 5-ASA may be a valid monotherapy in PSC-CD patients with a non-stricturing and non-penetrating disease that involves the colon. Larger cohorts and prospective studies are required to confirm our findings and mechanistic studies are needed to explore the mechanism of PSC in the context of IBD.

## CONCLUSIONS

In conclusion, this study demonstrates that CD patients with concomitant PSC are a clinically distinct population, characterized by predominant involvement of the colon, and a predominant non-stricturing and non-penetrating inflammatory phenotype, which is more reminiscent of UC patients. Future, larger and prospective studies are required to confirm these observations that may implicate a common pathogenesis between UC and PSC-CD patients and perhaps a need for a different clinical approach to this distinct population in terms of therapy and surveillance.

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**Correspondence**

**Dr. N. Maharshak**

Dept. of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel

**Phone:** (972-3) 694-7305

**Fax:** (972-3) 697-4184

**email:** nitsanm@tlvmc.gov.il

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## Capsule

### ADAM10-mediated ephrin-B2 shedding promotes myofibroblast activation and organ fibrosis

Maladaptive wound healing responses to chronic tissue injury result in organ fibrosis. Fibrosis, which entails excessive extracellular matrix (ECM) deposition and tissue remodeling by activated myofibroblasts, leads to loss of proper tissue architecture and organ function; however, the molecular mediators of myofibroblast activation have yet to be fully identified. **Lagares** and co-authors identified soluble ephrin-B2 (sEphrin-B2) as a new profibrotic mediator in lung and skin fibrosis. The authors provided molecular, functional, and translational evidence that the ectodomain of membrane-bound ephrin-B2 is shed from fibroblasts into the alveolar airspace after lung injury. Shedding of sEphrin-B2 promotes fibroblast chemotaxis and activation via EphB3 and/or EphB4 receptor signaling. They found that mice lacking ephrin-B2 in fibroblasts are protected from skin and lung fibrosis and that a disintegrin and metalloproteinase 10 (ADAM10) is the major ephrin-B2 sheddase in fibroblasts. ADAM10 expression is increased by transforming growth factor (TGF)-β1, and ADAM10-mediated sEphrin-B2 generation is required for TGF-β1-induced myofibroblast activation. Pharmacological inhibition of ADAM10 reduces sEphrin-B2 levels in bronchoalveolar lavage and prevents lung fibrosis in mice. Consistent with the mouse data, ADAM10–sEphrin-B2 signaling is upregulated in fibroblasts from human subjects with idiopathic pulmonary fibrosis. These results uncover a new molecular mechanism of tissue fibrogenesis and identify sEphrin-B2, its receptors EphB3 and EphB4 as well as ADAM10 as potential therapeutic targets in the treatment of fibrotic diseases.

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Eitan Israeli