Clinical Factors Associated with the Development of Crohn's Disease in Inflammatory Bowel Disease-unclassified Patients Undergoing Ileal Pouch–anal Anastomosis

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Background: Patients with inflammatory bowel disease-unclassified (IBDU) undergoing ileal pouch–anal anastomosis (IPAA) are at the risk of developing Crohn's disease (CD) after surgical procedure. In these patients, a *clinically* centered set of preoperative risk factors has not been prospectively defined. We report a single-center analysis of clinical factors associated with the development of CD after IPAA.

Methods: Consecutive IBDU patients undergoing IPAA were identified. The diagnosis of IBDU was based on the presence of atypical disease distribution, presence of granulomas on endoscopic biopsy, and/or perianal disease. The diagnosis of CD after IPAA included the presence of afferent limb inflammation on pouchoscopy in the absence of nonsteroidal anti-inflammatory drug use and/or the development of pouch fistulizing disease more than 3 months after ileostomy closure.

Results: Of the 149 study patients, 33 (22%) were diagnosed with CD after IPAA at a median of 37 months (interquartile range, 11–83 mo) after ileostomy closure. CD was diagnosed by mucosal inflammation above the pouch (n = 23; 70%), pouch fistulizing disease (n = 4; 12%), anorectal septic complications (n = 2; 6%), or the presence of ≥2 of the above complications (n = 4; 12%). The sole clinical predictor for the development of CD after IPAA was younger age at disease onset even after controlling for relevant clinical factors in a multivariate analysis. The odds of developing CD increased by 4% for each year that IBDU was diagnosed at a younger age.

Conclusions: Younger age at disease onset is the only clinical factor associated with the development of CD after IPAA for IBDU. Patients with IBDU undergoing IPAA with young age at disease onset should be counseled about the potentially higher risk of developing CD.

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Key Words: inflammatory bowel disease-unclassified, Crohn's disease, ileal pouch–anal anastomosis

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the standard operative approach for ulcerative colitis (UC) patients with medically refractory disease or dysplasia or cancer. Patients with inflammatory bowel disease-unclassified (IBDU) or indeterminate colitis (IC) are treated in a similar manner because it has been shown that their functional outcome, pouch survival rates, and quality of life are equivalent after IPAA, albeit with a higher rate of conversion to Crohn's disease (CD).[1–3] In a prospective study, our group has more recently demonstrated similar outcomes in the incidence of acute or chronic pouchitis and even in de novo CD after IPAA for IBDU or UC.[2] However, those studies that analyze only patients who develop CD after IPAA for IBDU, IC, and Crohn's colitis have reported different outcomes.[4–6]

Several studies have examined patient populations with the preoperative diagnoses of both UC and IBDU, and they have identified family history of CD and preoperative anti–*Saccharomyces cerevisiae* IgA seropositivity as predictive factors for the development of CD after IPAA.[7] A longer duration since IPAA and exposure to smoking were also identified as potential risk factors for CD of the pouch.[8] However, risk factors for the development of CD in patients with the preoperative diagnosis of IBDU remains largely unknown. In this study, we investigated the association of a clinically centered set of preoperative variables with the development of CD after IPAA in patients with IBDU.

METHODS AND ETHICAL CONSIDERATION

Study Population

Consecutive IBDU patients requiring proctocolectomy and IPAA for medically refractory disease or dysplasia and cancer from 1991 to 2014 were identified from a prospectively maintained, longitudinal, surgical database, which consisted of all

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patients with the preoperative diagnosis of UC or IBDU. All patients had a complete mucosectomy and a temporary diverting ileostomy at the time of IPAA creation. A single surgeon (P.R.F.) performed these procedures. Only patients who had their diverting stoma closed were included. Follow-up examination with a pouchoscopy was performed every 3 months in the first year after the closure of the diverting ileostomy and yearly subsequently. Approval for all research-related activities was obtained from the Institutional Review Board of the Cedars-Sinai Medical Center (IRB #3358).

Assessment of Clinical Characteristics

Preoperative clinical profiles for patients were prospectively collected using chart review and patient interview. Patient factors included gender, age at surgery, smoking history, family history of inflammatory bowel disease (IBD) (specifically CD), and the length of follow-up after closure of the diverting ileostomy. Patients who smoked at the time of surgery or who had quit smoking before colectomy were considered to be smokers. Preoperative disease factors analyzed were age of disease onset, duration and anatomical extent of disease, presence of perianal disease, concurrent small bowel inflammation, backwash ileitis or extraintestinal disease manifestations, thrombocytosis, crypt-associated granuloma noted on preoperative mucosal biopsies, and indication for surgery. Age of disease onset was measured from the time when IBD-specific symptoms were noted, which resulted in the final diagnosis. Disease duration was defined by the time interval between the diagnosis of IBD and surgery. Anatomical extent of the disease was postoperatively categorized as pancolitis, left-sided colitis, and proctitis. Perianal disease included a history of an anal fistula or ulcer, which was inactive at the time of surgery. The presence of small bowel inflammation was based on the results of wireless capsule endoscopy, computed tomography enterography, magnetic resonance enterography, and/or contrast small bowel follow-through. Presence of backwash ileitis was defined by both macroscopic and histologic inflammation in the distal 3 cm of the terminal ileum not thought to be CD. Extraintestinal manifestations noted before colectomy included primary sclerosing cholangitis (PSC), skin lesions (pyoderma gangrenosum, erythema nodosum), bone/joint disease (arthritis, ankylosing spondylitis, sacroiliitis), or eye disease (uveitis, episcleritis) the investigators and the patients' physicians consider to be manifestations of IBD. The diagnosis of PSC was based on clinical findings and confirmed in all cases using liver biopsy. Thrombocytosis was defined as platelet count $>450 \times 10^9$/L based on the blood drawn on the day of surgical procedure. Crypt-associated granuloma was defined as epitheloid noncaseating granuloma–related rupture of crypts secondary to inflammation. Serologic and genetic data, in addition to intraoperative and postoperative variables, were intentionally excluded from the analysis to fulfill the primary objective of conducting a clinically centered preoperative predictive analysis.

The diagnosis of IBDU was based on either the presence of one or a combination of the following: atypical disease distribution (skip lesions possibly related to previous therapy), small bowel inflammation (more than 3 cm from the ileocecal valve), crypt-associated granulomas on endoscopic biopsy, and/or the presence of perianal disease. CD after IPAA was diagnosed when patients developed either mucosal inflammation (5 or more ulcers) in the afferent limb above the pouch or perianal fistulizing disease more than 3 months after the closure of the diverting ileostomy.[9] Patients with exposure to nonsteroidal anti-inflammatory drugs, *Clostridium difficile* infection, or cytomegalovirus infection of the pouch were excluded.[10,11]

Statistical Analysis

Summary statistics to describe the data are represented by the numbers and percentages, mean and standard deviations, or the median and range, where appropriate. Comparisons between population means were performed using a 2-sample Student's *t* test for normally distributed variables. Otherwise, the Mann–Whitney test was used to compare population medians. Fisher's exact test was used to compare population proportions. Logistic regression model was used to further investigate the association between the development of CD and clinical factors. Multivariable logistic regression was further used to evaluate the association between the development of CD and clinical factors. All statistical analyses were performed in R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria), Significance was set a priori at $P < 0.05$.

RESULTS

From the database of patients for which a total of 551 patients from July, 1991 to June, 2014 underwent total proctocolectomy and IPAA by a single surgeon, 177 patients (32%) were classified as having IBDU. Of these patients, 28 were excluded as a result of incomplete data set. The remaining 149 study patients had a median age of 38 years (interquartile range [IQR], 25–50 yr) (Table 1). IBDU was diagnosed based on atypical disease distribution (n = 97, 65%), concurrent small bowel inflammation (n = 19, 13%), perianal disease (n = 22, 15%), or crypt-associated granuloma (n = 11, 7%). Just more than half (n = 84, 56%) of the study cohort was male. Median age at disease onset was 27 years (IQR, 18–37 yr) with a median disease duration of 60 months (IQR, 24–156 mo). The majority of patients had no exposure to smoking (n = 112, 75%) and no family history of inflammatory bowel disease (n = 111, 74%). A family history of CD occurred in only 12 patients (8%) within the study cohort. Most patients had pancolitis (n = 129, 87%) with the remaining 20 patients (13%) having disease limited to the left side of the colon. Thirty-three patients (22%) had extraintestinal manifestations, including 8 (5%) with PSC. Thrombocytosis was present in 27% of the study cohort (n = 40). The indication for surgical procedure was medically refractory disease in 129 patients (87%) with the remaining 20 patients (13%) having surgery for dysplasia and/or cancer.

After a median follow-up of 37 months (IQR, 11–83 mo) after stoma closure, 33 patients (22%) developed CD. Twenty-three patients (70%) developed mucosal inflammation above the pouch, 4 (12%) developed pouch fistulizing disease, and 2 (6%)

TABLE 1. Demographic and Clinical Features of Study Cohort

	IBDU Study Cohort (n = 149)	De Novo CD (n = 33)	Non-CD (n = 116)	*P*
Clinical characteristics				
Male:female	84:65	21:12	63:53	0.4
Age, yr	38 (25–50)	32 (23–29)	38 (29–50)	0.3
Age of disease onset, yr	27 (18–37)	20 (17–28)	28 (19–39)	**0.004**
Disease duration, mo	60 (24–156)	50 (20–192)	61 (24–144)	0.7
Preoperative clinical features, n (%)				
Exposure to smoking	37 (25)	8 (24)	29 (25)	1
Family history of IBD	38 (26)	8 (24)	30 (26)	1
CD	12 (8)	3 (9)	9 (8)	0.7
Disease extent				1
Pancolitis	129 (87)	29 (88)	100 (86)	
Left-sided colitis	20 (13)	4 (12)	16 (14)	
Perianal disease	23 (15)	4 (12)	19 (16)	0.8
Extraintestinal manifestation				0.4
None	115 (77)	28 (85)	87 (75)	
1 or more system	34 (22)	5 (15)	29 (25)	
PSC	8 (5)	2 (6)	6 (5)	
Thrombocytosis	40 (27)	10 (30)	30 (26)	0.7
Preoperative workup				
WCE/MRE/CTE/SBFT	56 (38)	16 (48)	40 (34)	0.2
SB abnormalities	13 (9)	4 (12)	9 (8)	1
Backwash ileitis	38 (26)	8 (24)	30 (26)	0.5
Features of the diagnosis for IBDU, n (%)				
Atypical distribution	97 (65)	22 (67)	75 (65)	1
Perianal disease	22 (15)	4 (12)	18 (16)	0.8
Concurrent SB inflammation	19 (13)	4 (12)	15 (13)	1
Crypt-associated granulomas	11 (7)	3 (9)	8 (7)	0.7
Surgical characteristics				
2 staged	96 (60)	21 (64)	75 (65)	
3 staged	53 (40)	12 (36)	41 (35)	
Indication				0.7
Medically refractory	129 (87)	28 (85)	101 (87)	
Dysplasia/cancer	20 (13)	5 (15)	15 (13)	

All data presented in median (IQR) or n (%) as stated otherwise. Bold indicates statistically significant value.
CTE, computed tomogram enterography; MRE, magnetic resonance enterography; PSC, primary sclerosing cholangitis; SB, small bowel; SBFT, small bowel follow-through; WCE, wire capsule endoscopy.

developed anorectal septic complications. Four patients (12%) developed 2 or more of the above complications. Preoperative clinical factors between IBDU patients who developed CD were compared with those who did not develop CD (Table 1). The sole clinical factor associated with the development of CD was younger age of disease onset.

There was a near linear decrease in the probability of developing CD as the age of onset of IBDU increased. We extrapolated that with every year younger in the age of disease onset, there was a 4% increase in the odds of developing CD after IPAA (Fig. 1). On stratifying the patients to those 20 years or younger (n = 54; 36%) and those 21 years or older, and after controlling gender, extraintestinal manifestation and methods of preoperative workup in a multivariate analysis, the younger age of disease onset was still associated with the development of CD (Table 2). The odds ratio (OR) of developing CD in the younger age group was 3.1 ($P = 0.006$).

DISCUSSION

In the current literature, the actual outcomes of patients with IBDU or IC undergoing IPAA remain controversial—some

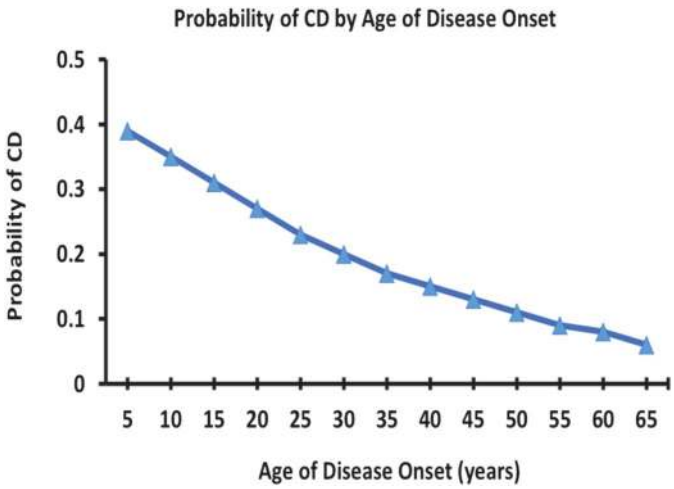

FIGURE 1. Probability of CD by the age of onset of IBDU.

reporting similar outcomes,[1–3] others reporting worse outcomes.[5,6] Several studies that examined only the select group of patients who eventually converted to CD after IPAA for both IBDU and Crohn's colitis were associated with poorer outcomes, with the quality of life significantly lower[4] and a pouch failure rate up to 45%.[5,6] These results are indicative of poorer outcome, which are to be expected in patients with newly established CD after IPAA. To our current knowledge, there has not been a study that looked only at the clinical predictors for CD in patients with the preoperative diagnosis of IBDU. From this selected group of patients, our results demonstrated that the only significant clinical predictor for the development of CD after IPAA was the younger age at disease onset.

We attempt to hypothesize why a younger age of disease onset placed surgical patients requiring IPAA for IBDU at a higher risk of developing CD: First, the natural disease and hence disease phenotype for these patients may be different—patients diagnosed at a younger age or in childhood may be exposed or respond differently to various microbial antigens as compared with adults, resulting in a more persistent immune reactivity.[12] Second, this may represent a function of time because the longer duration of microbial antigen exposure may increase eventual the rate of conversion. Our previous report of 97 patients demonstrated the development of CD in 14% of IBDU patients over a median follow-up time of 26 months after stoma closure.[2] In the current study, with the addition of another 52 patients, CD development was much higher (22%). This observation may reflect an increased incidence of CD with longer follow-up after IPAA.[4–6] Our findings corroborate the higher incidence of IBDU and higher conversion to CD in a younger nonoperated pediatric population described in a Canadian cohort study.[13] Based on our IBDU definition, the preoperative diagnosis of IBDU made up 32% of the IBD population in our surgical database. We acknowledge that this is higher than the reported incidence of 5% to 15% in other series,[14] but this may be related to the inclusion of pediatric patients in our series because many population-based studies have consistently found that the frequency of IBDU and IC to be approximately 2 times more in the pediatric population as compared with the adult population.[15]

In unoperated IBD patients, the likelihood of conversion from IBDU to CD was 14% in those whose diagnosis was made before 6 years of age, and it increased to 28% in those whose diagnosis was made at or after 10 years of age.[13] This is contrary to our findings that for every year younger the diagnosis of IBDU was made, the risk of developing CD increases. This may be due to several reasons. First, our study population was made up of a select group of IBDU patients who all required surgical procedure as compared with a general cohort of IBD patients. Second, those whose age of onset of disease was 10 years or younger made up to only 9% of our study population. In the pediatric population, those who were diagnosed with IBD before the age of 6 years were also reported to have had lower rates of surgical procedure than those diagnosed at 10 years and older. This leads us to believe that select patients with IBDU who require IPAA for disease control represent a different phenotype compared with the general population of patients with IBDU. Also, the longer duration of disease exposure in this group of patients may result in the eventual conversion to CD, which may imply that with longer follow-up, the rate of conversion will increase.

There may be other reasons for our results. Referral center bias must be considered, and also our definition of patients with IBDU may differ from other IBD centers, which had reported different results.[14] We acknowledge the inherent problem of the lack of consensus on the definition of IBDU as a disease entity,[16–19] but as a tertiary IBD center, we have consistently used the above definition for our practice. In patients with a preoperative diagnosis of IBDU, it would not be unexpected that the rate of developing CD be higher than the estimated 1% to 10% reported in other series of patients that included both UC and IBDU.[1,8,20] The prevalence of CD after IPAA in our study of IBDU was 22%, as compared with other series that report 6% to 14% in the adult population.[1,2] Mechanisms for this conversion remain unknown, and this is further complicated by controversies in the definition of IBDU. Some consider IBDU "an interim or

TABLE 2. Clinical Parameter Estimates from Multivariate Logistic Regression for Developing CD

Clinical Parameter	Estimate	OR	95% Confidence Interval	*P*
Age of disease onset, yr	1.14	3.14	1.40–7.19	**0.006**
Sex, male	0.34	1.40	0.62–3.29	0.43
Extraintestinal manifestation	0.18	1.20	0.42–3.94	0.75
WCE/MRE/CTE/SBFT	−0.51	0.60	0.26–1.37	0.22

Bold indicates statistically significant value.
CTE, computed tomogram enterography; MRE, magnetic resonance enterography; SBFT, small bowel follow-through; WCE, wire capsule endoscopy.

preliminary appellation rather than a distinctive entity," making the diagnosis of IBDU a temporary or provisional one rather than a definitive diagnosis.[21–23] Another definition of IBDU, proposed by Geboes and de Hertogh,[19] is based on the presence of these following features: clear evidence of IBD but insufficient to made a definite diagnosis of either UC or CD; clinical and macroscopic features of either disease entity without clear definitive histologic features of inflammatory colitis containing both macroscopic and microscopic features consistent with both UC and CD, colitis without a cause that can be conclusively identified, and clinical features of both UC and CD; mucosal UC with skip lesions, transmural inflammation, granulomata, or mucin depletion but not radiologic or clinical features of CD. It is evident that the variations in the definitions for IBDU can be either too stringent or all encompassing, including as many permutations of the various features that cannot be classified as either UC or CD.[16–18] With such a varying background, it is not surprising that the mechanism of this conversion of IBDU to CD remains elusive and difficult to investigate.

Finally, our results may reflect that as an IBD surgery team, we may be more aggressive in performing IPAA for IBDU as compared with other institutions especially because we did demonstrate that the long-term outcomes of the ileal pouch were similar in patients with UC or IBDU who underwent IPAA.[2]

From the results of our study, we have come to realize that factors previously found to be predictive of CD in patients undergoing IPAA for both UC and IBDU, such as perianal disease, smoking, and family history of IBD or CD, do not appear to be risk factors in this exclusive study of IPAA for IBDU. Thus, when counseling a patient with IBDU requiring colectomy, the only significant predictive factor for the development of CD after surgical procedure is a younger age of disease onset. We identified that the OR of developing CD on subsequent follow-up nearly doubled between those whose disease was diagnosed at the age of 20 years or older compared with those 18 years or younger (3.1 versus 1.8). This is interesting because the definition of adulthood varies between 18 and 21 years. Between these 2 age groups, there may be environmental factors that place those 18 years or younger to the greater risk of developing CD. Subgroup analysis of the incidence of CD was 32% in those with disease onset younger than 18 years and 40% in those whose disease onset was between 18 and 20 years of age. We realize that the numbers are small, but this may lead us to further examine any changes in both disease and environmental factors between these 2 groups of patients. This may also be an indicator for clinicians to do further testing involving genetics and seromarkers to better prognosticate for this group of patients. This will enable us to counsel patients and adjust their expectations accordingly. This increased risk can be reasonably discussed, and preemptive measures of a more intensive follow-up can be arranged for this group of patients.

We do recognize the limitations of our study. It is a single center, single surgeon series with referral bias. Also, the classification of patients under the IBDU category may vary between different centers; hence, we acknowledge that further validation of our findings with a larger number of patients is necessary. Nonetheless, our findings have shed further light into the natural history of IBDU.

CONCLUSIONS

The results of our study demonstrate that the only preoperative clinical predictor for the development of CD after IPAA in patients with IBDU is younger age at the onset of disease. Our findings suggest that risk factors for the development of CD in patients with UC may not apply to those with IBDU, allowing us to extrapolate that IBDU may be a disease deserving an individualized approach and not be deemed as a group of patients who remain indeterminate. Patients with the diagnosis of IBDU undergoing IPAA with a young age at disease onset should be counseled about a potentially higher risk for developing CD after IPAA, their expectations and postoperative surveillance managed as such. Patients in the pediatric age group (<18 to 20 yr of age) diagnosed with IBDU may represent a group with a different disease phenotype compared with those whose disease developed during adulthood. More importantly, a universally accepted definition for IBDU especially in the adult population will be of utmost value in further studying both the natural history and evaluation therapeutic response in this group of patients. Also, pediatric-onset IBDU requiring surgical intervention in the form of IPAA may represent a different disease phenotype compared with adult-onset IBDU.

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