TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS
TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

TJG
The Turkish Journal of Gastroenterology

Rate and predictive factors of post-IPAA Crohn's-like disease (with or without pouchitis) in patients with ulcerative colitis

Ülseratif kolit tanısı ile ileal poş anal anostomoz sonrası Crohn benzeri perianal hastalığın (poşit ile veya poşitsiz) oranı ve prediktif faktörleri

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INTRODUCTION

Ileal pouch-anal anastomosis (IPAA) has become the standard operative approach for patients requiring colectomy for ulcerative colitis (UC). Despite excellent functional results and high patient satisfaction (1,2), approximately 5-10% of patients develop Crohn's disease (CD) of the pouch (3-8). While some authors assume the above-described situation to be CD (9), others accept this as a phenotype of UC mimicking CD (10). Therefore, they refer to the condition as Crohn's-like disease (CLD). The presence of extraintestinal involvement may increase the frequency of CLD following IPAA (11). According to their retrospective assessment, those who disapprove the diagnosis of CD have claimed that the clinical picture and symptoms were suggestive of UC from the beginning. On the contrary, some authors claim that the presence of the typical clinical and morphological characteristics of CD in cases with fistula formation is an obvious evidence of CD.

When the final diagnosis could not be made with the current clinical and morphological findings, additional laboratory and serological evaluations have been discussed. Serological immune markers have been associated with inflammatory bowel disease (IBD). Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are found in 60-80% of patients with UC (12-14). p-ANCA is also present in 15-25% of patients with CD (12). Anti-Saccharomyces cerevisiae antibodies (ASCA) are found in approximately 60% of CD patients (16,17). Although serum p-ANCA and ASCA are the most frequently investigated serologic markers in IBD, antibodies against outer membrane porin C (anti-OmpC) of *Escherichia coli* and anti-CBir1 are also found in approximately 50% of patients with CD and to a lesser degree in patients with UC (18,19). The clinical importance of these disease markers in terms of predicting development of CD following IPAA is not defined yet. In previous studies, as many as 3.5-9% of all patients who underwent total proctocolectomy and IPAA for UC were diagnosed as CD following surgery, characterized by the development of severe pouchitis or by strictures, abscesses, sinus tracks, or fistulas involving the pouch or distal ileum (20-24). However, the value of preoperative ileal intubation with or without ileal punch biopsy, in the preemptive diagnosis of undetermined colitis or CD before colectomy, has not been determined. Therefore, the value of these parameters remains a matter of debate.

Pouchitis is the most common complication of IPAA in UC patients, presenting as nonspecific inflammation of the ileal reservoir. Extensive colitis, extraintestinal involvement (particularly primary sclerosing cholangitis), nonsmoker status, p-ANCA positivity, and use of non-steroidal antiinflammatory drugs (NSAIDs) are risk factors for pouchitis (25).

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Manuscript received: 01.08.2012 **Accepted:** 27.08.2012

Turk J Gastroenterol 2012; 23 (Suppl. 2): 30-34
doi: 10.4318/tjg.2012.0621

The etiology of pouchitis is not known; it emerges following development of colonic metaplasia in the pouch (25). The histopathology is nonspecific, and it presents as an acute inflammation with polymorph nuclear leukocyte (PNL) infiltration. Risk of development of CD in the pouch increases with smoking and duration of pouch (25).

Preoperative predictors for CD post-IPAA have not been prospectively defined, and we investigated the association of preoperative clinical and serologic factors with the development of CD after IPAA. The aim of this literature search was to determine the frequency of this occurrence, and to identify predictive factors leading to a CD diagnosis.

In this article, for the post-IPAA-related new clinical condition, we used the term "Crohn's- like disease" without using definitions such as "Crohn's disease" or "Crohn's disease mimicking the UC phenotype".

MATERIALS AND METHODS

A systematic literature search was performed in the PubMed database. Questions were designated as follows: 1-What percentage of patients is diagnosed as CLD following colectomy for UC? 2- What are the initial predictive parameters in these patients? Keywords used were as follows: ("Crohn Disease"[Mesh] AND "Colitis, Ulcerative"[Mesh]) AND (colectomy OR surgery OR ileal pouch-anal anastomosis OR pouchitis OR fistulae). All the literature we assessed was written in English and dated between 1970 and 2010. A total of 2111 publications were found; 2069 were excluded following title/abstract screening, and 19 were excluded following full text review. The remaining 23 reports, five being prospective and 18 retrospective, were analyzed. Reports published in languages other than English, case presentations, and studies with insufficient statistical data were excluded from the present trial.

RESULTS

Analysis of retrospective trials disclosed the rate of patients pre-diagnosed as UC and diagnosed as CLD following IPAA as 5.2% (307/5899) (range: 1-31%). Among this group, the percentage of cases with fistula was 172/307 (56%) (range: 12%-100%) and the rate of non-fistulating cases was 139/307 (45%) (range: 14-100%). In the analysis of prospective trials, the percentage of patients pre-diagnosed as UC and diagnosed as CLD following IPAA was determined as 55/1028 (5.3%) (range: 2-37%). Among these cases, the number of patients with fistula was 29/55 (52%) (range: 25-92%) and with non-fistulating CLD was 26/55 (47%) (range: 7%-100%) (Table 1). In the studies of Melmed (39) and Evers (26), the following values were determined as predictive factors for postoperative development of CD: ASCA IgA: odds ratio (OR): 4.2 (95% confidence interval [CI]: 1.485-11.981; p: 0.012) and for pANCA, OR: 3.8 (95%CI: 0.874-16.880; p: 0.074). Among factors predicting development of CLD following IPAA in cases pre-diagnosed as UC, OR was calculated as 1.3 for anti-OmpC, 1.4 for ASCA IgG and 0.5 for anti-CBir1. In the study conducted by Melmed et al. (39), presence of family history for CD was found to be a risk factor with OR: 8.9 (95%CI: 2.829-28.089; p: 0.0008). Accordingly, in a trial conducted by Melmed et al. (39), OR values for predictive factors were calculated as 0.7 for positive family history of UC, 1.1 for pancolitis and 0.9 for left-sided UC. In trials performed by Melmed et al. (39), correlation between gender and development of postoperative CLD was determined as OR: 1.1 for women and OR: 0.9 for men (24) (Table 2). Evers et al. (26), in their trial published in 2009, reported low weight Z score as a predictive factor for the development of CLD. In 2005, Prudhomme et al. (29) indicated that the rate of a possible diagnosis of CLD is increased in diseases of the small intestine, recurrent fistulae and abscess, mucosal ulceration, or perianal lesion. Female/male ratios in CLD with and without fistula were (74%/25%) and (44%/55%), respectively (Table 3). Extraintestinal manifestations were rare, with arthritis seen in only three patients and primary sclerosing cholangitis in only two patients.

CONCLUSION

Diagnostic differentiation between UC and CD is sometimes difficult, especially in the setting of

Table 1. Prevalence of patients postoperatively diagnosed as CLD (with or without perianal fistula formation) after colectomy for UC and the presentations of CLD

	UC→CLD	With fistula	Other presentations
*Retrospective	5.2% (range: 1%-31%)	56% (172/307) (range: 12%-100%)	45% (139/307) (range: 14%-100%)
**Prospective	5.3% (range: 2%-37%)	52% (29/55) (range: 25%-92%)	47% (26/55) (range: 7%-100%)

*References: 1, 20, 21, 26-38 **References: 24, 39-42 UC: Ulcerative colitis CLD: Crohn's-like disease

acute colitis, in which overlapping histological features may be present. Some clinicians have looked for cellular factors in addition to clinical and pathologic features to distinguish types of IBD. The use of ANCA analysis is, therefore, of limited value in differentiating CD from UC because of the high prevalence of ANCA-positive serum in patients with CD of the colon (2).

Dendrinos et al. (28) examined the association between the serologic markers, p-ANCA and ASCA and fistula formation in post-IPAA patients. They suggested that patients who were p-ANCA(-)/ASCA(+) were at increased risk for the development of fistulas postoperatively compared to patients who were p-ANCA(+)/ASCA(-). Postoperatively, this group was also more likely to have their diagnoses changed to CLD (OR: 19.2, 95% CI: 1.752-210.341, p: 0.00) (7) (Table 4).

Among patients being followed as UC, the diagnosis may be revised to CLD in up to 5% during the postoperative period (IPAA). At least half of these cases have distinctive criteria, which may enable an objective differentiation of CLD and pouchitis (perianal involvement, fistula, abscesses). Types and percentage of fistula of post IPAA CLD in previously UC diagnosed patients and percentage and presentation of post IPAA CLD in previously UC diagnosed patients wihout fistula are shown at Table 5 and Table 6. ASCA IgA is not sufficient for differentiating CD and UC, though in UC patients subjected to colectomy, it may be beneficial in predicting a new diagnosis of CD (10). ASCA IgA seropositivity compared to p-ANCA (-)/ASCA (+) status may be a stronger predictive factor for final diagnosis of CLD following IPAA in UC patients (16). Having a positive family history for CLD may be regarded as another predictive factor as well (3).

Table 2. Predictive parameters of post-IPAA CLD in previously UC-diagnosed patients

Predictive parameters	OR	p
ASCA IgA	4.2 95% CI: 1.485-11.981	p: 0.012
p-ANCA	3.8 95% CI: 0.874-16.880	p: 0.650
Anti-OmpC	1.3 95% CI: 0.514-3.712	p: 0.589
ASCA IgG	1.4 95% CI: 0.307-6.672	p: 0.650
Anti-CBir 1	0.5 95% CI: 0.126-2.636	p: 0.187
CD in family history	8.9 95% CI: 2.829-28.089	p: 0.0008
UC in family history	0.7 95% CI: 0.166-3.507	p: 1.00
Pancolitis	1.1 95% CI: 0.344-3.579	p: 1.00
Left colon UC	0.9 95% CI: 0.299-3.112	p: 1.00
Female	1.1 95% CI: 0.675-1.818	p: 0.704
Male	0.9 95% CI: 0.55-4.81	p: 0.704

References: 26, 39. IPAA: Ileal pouch-anal anastomosis. CLD: Crohn's-like disease. UC: Ulcerative colitis. ASCA IgA: Anti-Saccharomyces cerevisiae antibody Immunoglobulin A. p-ANCA: Perinuclear antineutrophil cytoplasmic antibodies. Anti-OmpC: Antibodies againts outer membrane porin C. ASCA IgG: Anti-Saccharomyces cerevisiae antibody Immunoglobulin G. CD: Crohn disease. UC: Ulcerative colitis: CI: Confidence interval.

Table 3. Sex of post-IPAA CLD in previously UC-diagnosed patients with fistula or other presentations

Patients	Fistula	Other presentations
Male	21/83 (25%)	50/90 (55%)
Female	62/83 (74%)	40/90 (44%)

IPAA: Ileal pouch-anal anastomosis. CLD: Crohn's like disease. UC: Ulcerative colitis.

Table 4. Comparison between p-ANCA(+) ASCA(-) and p-ANCA(–) ASCA(+) in UC patients in whom postoperative CD was diagnosed

	Pre-operative patient number	Postoperative- diagnosed CD	
p-ANCA(+) ASCA(-)	16	1	OR: 0.08 p: 0.008 95% CI: 0.0075-0.931
p-ANCA(–) ASCA(+)	9	4	OR: 12 p: 0.001 95% CI: 1.0737-134.1161

Reference: 33. p-ANCA: Perinuclear antineutrophil cytoplasmic antibodies. ASCA: Anti-Saccharomyces cerevisiae antibody. UC: Ulcerative colitis. CD: Crohn disease. OR: Odds ratio. CI: Confidence interval.

Table 5. Types and percentage of fistula of post-IPAA CLD in previously UC-diagnosed patients

Types of fistula	Patient number	Percentage
Pouch fistula	173/193	89%
Pouch-vaginal fistula	34/193	17%
Perianal fistula	16/193	8%
Pouch-perineal fistula	7/193	3%
Pouch-enteric fistula	2/193	1%
Anovaginal fistula	1/193	0.5%
Enterovaginal fistula	1/193	0.5%
Enterocutaneous fistula	1/193	0.5%
Ischiorectal fistula	1/193	0.5%
Perineoscrotal fistula	1/193	0.5%
High supralevator fistula	3/193	1%

IPAA: Ileal pouch-anal anastomosis. CLD: Crohn's like disease. UC: Ulcerative colitis.

Table 6. Percentage and presentation of post-IPAA CLD in previously UC-diagnosed patients without fistula

Ileum ulcer	27/70	38%
Ileum+pouch ulcer	17/70	24%
Ileal ulcer+stricture of the t. ileum	1/70	1%
Stricture of the ileoanal anastomosis	8/70	11%
Lymphoid aggregates, granulomas, transmural inflammation	7/70	10%
Granulomas in the colectomy specimens	10/70	14%

In conclusion, although endoscopic, radiologic and laboratory results fulfill the UC criteria in IBD patients before the colectomy, following the IPAA, diagnosis may change to CLD in 5% of these patients. CLD morphology with accompanying granuloma is a generally accepted indicator of CLD in a patient with previously diagnosed UC. However, low sensitivity of granuloma formation for the prediction of CD reduces its clinical value. Therefore, unless better indicators appear, existence of fistula is more suggestive of CLD for the clinician. Currently, it is obvious that we should treat CLD in the same way we treat CD with perianal and/or rectal involvement without paying unnecessary attention to whether the diagnosis is CLD or UC.

Recommendations:

What percentage of patients is diagnosed as CLD following colectomy for UC?

In 5% of patients with UC, following IPAA, the diagnosis may change to CLD. ***(EL 2b, RG B)***

What are the initial predictive parameters in these patients?

In patients with IBD, preoperative ASCA IgA positivity may be suggestive for postoperative CLD development. Concomitant existence of p-ANCA may further increase this possibility. ***(EL 2b, RG B)***

In patients who are candidates for IPAA, preoperative serologic tests (p-ANCA, ASCA) may help to predict postoperative CLD development. ***(EL 5, RG D)***

Presence of CD in the family can be another indicator for the development of CLD after IPAA. ***(EL 2b, RG B)***

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