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Follow-Up and Treatment Results in Penetrating Crohn's Disease

Penetran Crohn Hastalığında Takip ve Tedavi Sonuçları

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ABSTRACT

Background: To determine intestinal penetrating complications in patients with Crohn's disease (CD) and to retrospectively evaluate clinical characteristics, the frequency of accompanying stenosing and perianal complications, management strategies, and predictors of the need for surgical intervention.

Materials and Methods: Patients with CD complicated by penetrating intestinal manifestations, including sinus tracts, fistulas, phlegmon, and mesenteric or peritoneal abscesses, who were followed between 1986 and 2021, were included. Patients who developed penetrating complications after intra-abdominal interventions were excluded. Demographic, clinical, laboratory, and treatment data were recorded. Patients were classified into three groups: isolated abscess (IA), isolated fistula (IF), and an overlapping group (both an abscess and a fistula). Comparisons were performed among these groups.

Results: A total of 114 patients were evaluated: 18 (15.8%) had IAs, 35 (30.7%) had IFs, and 61 (53.5%) had both complications. Penetrating complications were detected in 84 of 114 patients during follow-up. Concomitant stenosis was more frequent in the overlapping group than in the other groups, although this difference did not reach statistical significance (80.3% vs. 55.6% and 65.7%; p = 0.075). The cut-off value of abscess size for predicting the need for surgical intervention was 2.75 cm. Patients with stenosis located in intestinal segments other than the fistula site had a 27.5-fold higher risk of requiring fistula surgery (p = 0.013). The rate of bowel resection was significantly higher in the overlapping group than in the IA and IF groups (70.5% vs. 27.8% and 28.6%, respectively; p < 0.001).

Conclusion: Penetrating complications occur frequently during follow-up in CD. Patients with both an abscess and a fistula have a worse prognosis, with a more severe clinical course and an increased likelihood of requiring surgical intervention.

Keywords: Abscess, complication, fistula, surgery

ÖZ

Amaç: Crohn hastalığı olan olgularda intestinal penetran komplikasyonların özelliklerini ortaya koymak ve klinik özellikleri, eşlik eden stenoz ve perianal komplikasyonların sıklığını, uygulanan tedavi yaklaşımlarını ve cerrahi gereksinimini öngören faktörleri retrospektif olarak değerlendirmek.

Gereç ve Yöntemler: Çalışmaya, 1986–2021 yılları arasında izlenen ve sinüs traktı, fistül, flegmon ile mezenterik veya peritoneal yerleşimli apse gibi intestinal penetran bulgularla komplike Crohn hastalığı tanısı olan hastalar dahil edildi. İntraabdominal girişimler sonrasında penetran komplikasyon gelişen olgular çalışma dışı bırakıldı. Hastaların demografik, klinik, laboratuvar ve tedaviye ilişkin verileri kaydedildi. Olgular üç grupta sınıflandırıldı: izole apse, izole fistül ve ortak grup (hem apse hem fistül bulunanlar). Gruplar arası karşılaştırmalar yapıldı.

Bulgular: Çalışmaya alınan 114 hastanın 18'inde (%15,8) sadece apse ve 35'inde (%30,7) sadece fistül saptanırken 61 hasta ortak gruptaydı. Yüz on dört hastanın 84'ünde penetran komplikasyonun takip sırasında ortaya çıktığı görüldü. Ortak gruptaki hastalarda, penetran komplikasyona eşlik eden darlık alanının varlığı diğer hastalık gruplarına kıyasla daha fazla olmakla birlikte, bu fark istatistiksel olarak anlamlı değildi (%80,3'e karşı %55,6 ve %65,7; p = 0,075). Apse açısından cerrahi operasyon için kesim noktası

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2,75 cm idi. Farklı segmentte darlık alanı olmasının fistül için cerrahi operasyon riskini 27,5 kat artırdığı istatistiksel anlamlılıkla gösterildi (p = 0,013). Ortak grupta bağırsak rezeksiyonu yapılma oranı diğer gruplara göre anlamlı derecede daha fazla saptandı (%70,5'e karşı %27,8 ve %28,6; p < 0,001).

Sonuç: Penetran hastalık çoğunlukla takip sırasında ortaya çıkmaktadır. Apse ve fistülün birlikte görüldüğü hastalar klinik gidiş ve cerrahi açısından daha kötü prognoza sahiptir.

Anahtar Kelimeler: Apse, komplikasyon, fistül, cerrahi

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that arises from dysregulated immune responses driven by the interaction of genetic susceptibility, environmental factors, and the intestinal microbiota (1). CD can involve any segment of the gastrointestinal tract in a discontinuous pattern and is characterized by recurrent transmural inflammation (2), which can lead to structural complications such as strictures, fistulas, and abscesses (3). Disease behavior is therefore classified according to the presence of these complications (4). The Montréal classification is widely used to define disease location and behavior, categorizing patients into inflammatory (B1), stricturing (B2), and penetrating (B3) phenotypes (5,6). Penetrating disease, which includes fistulas, intra-abdominal inflammatory masses, and abscesses, is reported to develop in approximately 40% of patients within five years of diagnosis (5,7).

Therapeutic goals extend beyond symptom control to include prevention of stricturing and/or penetrating complications that may necessitate surgical intervention (1,8). Thiopurines have not consistently reduced intestinal complication rates or the risk of surgical resection (9), whereas anti-tumor necrosis factor (anti-TNF) agents, owing to their superior effects on mucosal healing, have been associated with reduced rates of hospitalization and surgery (10). Infliximab has demonstrated efficacy in inducing and maintaining remission in both inflammatory and fistulizing diseases (11). These data emphasize the importance of identifying patients at increased risk for intestinal complications to guide timely treatment decisions (8).

In the penetrating phenotype, progressive transmural inflammation may result in sinus tracts or fistulas and evolve into phlegmon and, if infected, an abscess (12,13). Clinical manifestations vary by fistula location and the affected bowel segment (12,14). Non-perianal penetrating CD often requires complex management involving medical therapy, radiologically guided interventions, and surgery. However, evidence guiding the management of intestinal penetrating complications remains limited, and practice varies across inflammatory bowel disease (IBD) centers (12).

Accordingly, this study aimed to evaluate the frequency, spectrum, anatomical distribution, diagnostic approaches, and timing of non-perianal penetrating complications in CD; to identify risk factors independent of iatrogenic causes; to characterize management strategies; and to determine predictors of surgical intervention. Secondary aims were to examine the relationship between penetrating and stricturing disease and to determine the frequency of concomitant perianal disease in patients with intestinal fistulas.

Materials and Methods

Study Design

This retrospective cohort study was conducted at the IBD Outpatient Clinic of the Division of Gastroenterology, İstanbul University–Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Medical records of patients with CD who were followed from 1986 to 2021 were reviewed by examining outpatient charts and the hospital information system. Adult patients (≥18 years) with a definite diagnosis of CD and at least one documented intestinal penetrating complication were eligible for inclusion. Patients were excluded if penetrating complications developed after intra-abdominal surgery, radiological drainage of an intra-abdominal abscess, or endoscopic balloon dilatation for strictures. Additional exclusion criteria were: a CD diagnosis of less than 6 months' duration, follow-up at our center shorter than 6 months, insufficient medical records prior to the development of penetrating complications, and follow-up shorter than 6 months after the diagnosis of penetrating complications.

Demographic and disease-related data were recorded. Disease location at diagnosis was classified according to the Montréal classification (L1–L4) and further detailed using endoscopic and radiological findings. The presence of perianal disease at diagnosis and during follow-up was also documented. Baseline laboratory parameters were obtained at diagnosis or, if initial data were unavailable, during a complication-free period. Colonoscopic findings, including ulcer morphology, fistula openings, and strictures, were reviewed. Ongoing and previous medical therapies during

the three months preceding the diagnosis of penetrating complications were recorded, together with subsequent changes in treatment and any surgical or radiological interventions. For the purposes of analysis, anti-TNF and other biologic agents were considered not to have been administered if induction therapy was not completed. Immunosuppressive agents used for less than three months were also classified as not administered.

Definitions and Classification of the Disease Groups

Mesenteric or peritoneal sinus tracts, fistulas, phlegmons, and abscesses were defined as penetrating complications in accordance with current guideline-based definitions (13-16). Obstructive complications were defined as fixed luminal narrowing with or without prestenotic dilatation. Penetrating and obstructive complications documented by radiological or endoscopic methods were systematically reviewed; fistulas diagnosed based on typical clinical features (e.g., vaginal, cutaneous, or vesical) were also included.

For time-based assessment, strictures detected within one month before or after a penetrating complication were classified as concomitant, whereas those identified more than one month before the penetrating complication were considered preceding. Localization of strictures and penetrating lesions was determined by computed tomography (CT), CT enterography, and endoscopy.

Patients were categorized into three groups: isolated abscess (IA), isolated fistula (IF), and an overlapping group (both an abscess and a fistula). Because fistulas that developed shortly after abscess diagnosis, without any intervention, were considered pathophysiologically related, these patients were further classified as the "abscess-associated fistula" subgroup. Accordingly, four groups (IA, IF, abscess-associated fistula, and others) were used for analysis of risk factors and prognosis. For abscess-related analyses, the IA and abscess-associated fistula groups were evaluated together.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± standard deviation or median (minimum–maximum), as appropriate. The Shapiro–Wilk test was used to assess normality. Categorical variables were compared using the Pearson chi-square, Fisher's exact, or Fisher–Freeman–Halton tests. Continuous variables were compared using the Student's t-test or the Mann–Whitney U test for two-group comparisons, and the Kruskal–Wallis test for multiple groups, with Dunn's test for post-hoc analyses. Variables significant in univariate analyses were included in multivariable binary logistic regression models. Model fit was assessed using the Hosmer–Lemeshow test and explanatory power was assessed using the Nagelkerke R^2. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of abscess size to predict the need for surgery by calculating the area under the curve (AUC). The optimal cut-off value was determined using the Youden index. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS software (version 28).

Ethic

Ethical approval was obtained from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (approval number: 189, approval date: 31.05.2022).

Results

Among 1,404 patients with CD followed at our center, penetrating complications were identified in 312. Of these, 112 patients with a history of intra-abdominal surgery or radiological intervention prior to the development of the fistula and 86 patients who met the exclusion criteria were excluded. Consequently, a total of 114 patients were included in the final analysis. Of the 114 patients included in the analysis, 59 were female and 55 were male. The mean age was 40.6 ± 13.1 years. At the time of CD diagnosis, penetrating complications were present in 30 patients (26.3%), and perianal disease was identified in 25 patients (21.9%). The mean interval from CD diagnosis to the development of penetrating complications was 39.7 ± 45.7 months. The demographic and clinical characteristics of the study population are summarized in Table 1.

Patients were categorized into three groups according to the type of penetrating complication: IA, IF, and an overlapping group with both an abscess and a fistula. The numbers of patients in these groups were 18 (15.8%), 35 (30.7%), and 61 (53.5%), respectively. Within the overlapping group, 26 patients who developed a fistula within three months of abscess diagnosis without intervention were further classified as the abscess-associated fistula subgroup.

Clinical Features of IA, IF, and Overlapping Groups

In the IA group (n = 18), 10 patients were female and 8 were male. The mean age was 42.9 ± 13 years (median 41; range 25–75), and the mean CD duration was 128 ± 68.5 months (median 114; range 24–252). The mean abscess size was 3.4 ± 1.7 cm (median, 3.4 cm; range, 1–7 cm). Abscesses were most frequently located in the ileocecal region (n = 11), followed by bowel-segment-related locations (n = 2), muscle-related locations (n = 2), pelvic locations (n = 1), combined ileocecal and muscle locations

(n = 1), and combined ileocecal and pelvic locations (n = 1). Concomitant obstructive complications were present in 10 patients (55.6%); in three of these patients, obstruction was detected concomitantly with the abscess, whereas in the remaining patients, it had been documented before the abscess diagnosis. Antibiotic therapy was administered to all but two patients, with a mean treatment duration of 5.1 ± 4.6 weeks (median, 3 weeks; range, 1–15 weeks). In addition to antibiotics, medical treatment was modified in 11 patients (61.1%): azathioprine was added to six patients, infliximab to one patient, adalimumab to one patient, combination therapy with azathioprine and an anti-TNF agent (adalimumab or certolizumab) to two patients, and oral mesalazine to one patient. Regarding interventional management, no invasive procedures were required for 10 patients, whereas three patients underwent surgery alone, three patients underwent radiological drainage alone, and two required both radiological drainage and subsequent surgery.

In the IF group (n = 35), 19 patients were female and 16 patients were male. The mean age was 41.6 ± 14.9 years (median 40 years; range 21–75 years), and the mean CD duration was 150.1 ± 74.6 months (median 144 months; range 24–324 months). Multiple fistulas were detected in six patients (17.1%). Regarding fistula types, enteroenteric fistulas were observed in 5 patients, enterocolic fistulas in 12 patients, colocolic fistulas in 4 patients, cutaneous fistulas in 1 patient, vesical fistulas in 1 patient, vaginal fistulas in 9 patients, ureteral fistulas in 1 patient, and combined enteroenteric and enterocolic fistulas in 2 patients. Fourteen patients (40%) underwent surgical intervention for fistula management. Among the 21 patients managed without surgery, medical therapy was modified in 12: anti-TNF treatment was initiated or intensified in nine, and azathioprine was added in three. Specifically, infliximab was initiated in four patients; certolizumab was used as monotherapy in one patient; infliximab or adalimumab were administered in combination with azathioprine in three patients; and infliximab dose escalation was performed in one patient. Risk factors for surgical intervention in patients with fistulizing CD were evaluated using univariate and multivariable analyses. In univariate analysis, increasing age and the presence of a stricture (either in the same or in a different intestinal segment from the fistula) were associated with a higher risk of surgery. Each one-year increase in age was associated with a 1.05-fold increase in surgical risk (p = 0.05); the presence of a stricture in a different segment was associated with a markedly increased risk (odds ratio

Table 1. Baseline demographic and clinical characteristics of patients with penetrating CD.

Baseline variables	Patients, n = 114
Gender, n (%) Female Male	 59 (51.8) 55 (48.2)
Age (years)	40.6 ± 13.1 (20–75)
Age at diagnosis (years)	29 ± 11.5 (14–72)
Disease duration (months)	143.9 ± 74.3 (16–420)
Time from symptom onset to CD diagnosis (months)	19.9 ± 36.9 (0–192)
Time from CD diagnosis to penetrating complication (months)	39.7 ± 45.7 (0–200)
Disease location at diagnosis (Montréal), n (%) Ileal (L1) Colonic (L2) Ileocolonic (L3) L4 (upper GI involvement)	 29 (25.4) 29 (25.4) 53 (46.5) 3 (2.6)
Smoking status, n (%) Never smoker Former smoker Current smoker	 49 (43) 23 (20.2) 42 (36.8)
Penetrating complication at diagnosis, n (%)	30 (26.3)
Perianal disease at diagnosis, n (%)	25 (21.9)
Perianal disease during follow-up, n (%)	24 (21.1)
Presence of obstructive segment, n (%) Absent prior to penetrating complication Present prior to penetrating complication Concomitant with penetrating complication	 32 (28.1) 53 (46.5) 29 (25.4)

Results are presented as mean ± standard deviation (range) or n (%), as appropriate. CD, Crohn's disease; GI, gastrointestinal.

[OR] = 27.5; p = 0.013). The presence of multiple fistulas was not significantly associated with surgical risk (OR 1.64; p = 0.585). Neither current nor prior use of azathioprine or corticosteroids was associated with the need for surgery. In multivariable binary logistic regression analysis, only the presence of strictures remained independently associated with surgical risk. A stricture located in a segment different from the fistula increased the risk of surgery 454.3-fold (p = 0.019), whereas a stricture located in the same segment increased the risk 70.7-fold (p = 0.042).

In the overlapping group (n = 61), 30 patients were female and 31 were male. The mean age was 39.2 ± 12.0 years (range, 20–71 years), and the mean CD duration was 145.1 ± 76.3 months (range, 16–420 months). Among these patients, 26 were classified as having an abscess-associated fistula. In this subgroup, 15 patients (57.7%) had a single fistula. Of the 26 patients with abscess-associated fistulas, seven did not undergo surgical intervention. Among these patients, medical therapy was modified in two patients by the addition of infliximab combined with azathioprine.

Comparison of Clinical Characteristics and Outcomes Between Groups

Clinical characteristics and outcomes were compared across the four groups—IAs, IFs, abscess-associated fistulas, and the remaining overlapping group—and are presented in detail in Table 2. Sex distribution, age at diagnosis, and disease duration were similar among groups (p = 0.24, p = 0.586, and p = 0.718, respectively). According to the Montréal classification, colonic involvement (L2) at diagnosis was significantly more frequent in the IF group than in the overlapping group–other subgroup (40% vs. 11.4%; p = 0.036). The presence of penetrating complications at diagnosis and the interval from CD diagnosis to the development of penetrating complications did not differ between groups (p = 0.484 and p = 0.521, respectively). Likewise, the prevalence of perianal disease and concomitant strictures at diagnosis were comparable across groups (p = 0.224 and p = 0.142). Baseline laboratory parameters were similar among groups (all p > 0.05). No significant differences were observed in colonoscopic findings, including ulcer morphology, strictures, and fistula openings (all p > 0.05).

Regarding prognosis, bowel resection rates were significantly higher in the abscess-associated fistula, overlapping, and other subgroups compared with the IA and IF groups (p < 0.001). The diverting ostomy rate was significantly lower in the abscess-associated fistula group (3.8%; p = 0.012) than in the other three groups, whereas the prevalence of permanent ostomy was similar across

Table 2. Comparison of clinical characteristics and outcomes across penetrating phenotypic groups.

	IA, n = 18	IF, n = 35	Abscess-associated fistula, n = 26	Overlapping group–others, n = 35	p-value
Gender, n (%) Female Male	 10 (55.6) 8 (44.4)	 19 (54.3) 16 (45.7)	 9 (34.6) 17 (65.4)	 21 (60) 14 (40)	0.24
Age (years)	42.9 ± 13 (25–75)	41.6 ± 14.9 (21–75)	38.3 ± 12.4 (20–62)	39.8 ± 11.7 (22–71)	0.759
Age at diagnosis (years)	32.8 ± 13.8 (17–72)	29.8 ± 13 (14–63)	27.3 ± 9.1 (14–51)	27.5 ± 9.9 (15–56)	0.586
Disease duration (months)	128 ± 68.5 (24–252)	150.1 ± 74.5 (24–324)	138.1 ± 77 (19–276)	150.2 ± 76.4 (16–420)	0.718
Time from symptom onset to CD diagnosis (months)	20.8 ± 32.8 (0–120)	15.6 ± 25.3 (0–120)	25.4 ± 51.6 (0–192)	19.9 ± 36.8 (0–180)	0.958
Smoking status, n (%) Never smoker Former smoker Current smoker	 7 (38.9) 6 (33.3) 5 (27.8)	 14 (40) 6 (17.1) 15 (42.9)	 12 (46.2) 6 (23.1) 8 (30.8)	 16 (45.7) 5 (14.3) 14 (40)	0.707
Family history of IBD, n (%)	0 (0)	5 (14.3)	2 (7.7)	5 (14.3)	0.346
Disease location at diagnosis (Montréal), n (%) Ileal (L1) Colonic (L2) Ileocolonic (L3) L4 (upper GI involvement)	 8 (44.4) 3 (16.7) 6 (33.3) 1 (5.6)	 4 (11.4) 14 (40) 16 (45.7) 1 (2.9)	 8 (30.8) 8 (30.8) 10 (38.5) 0 (0)	 9 (25.7) 4 (11.4) 21 (60) 1 (2.9)	**0.036**
Penetrating complication at diagnosis, n (%)	6 (33.3)	11 (31.4)	7 (26.9)	6 (17.1)	0.484

Table 2. Continued.

	IA, n = 18	IF, n = 35	Abscess-associated fistula, n = 26	Overlapping group–others, n = 35	p-value
Time from CD diagnosis to penetrating complication (months)	33.1 ± 50.5 (0–180)	38.6 ± 46.3 (0–200)	37.4 ± 40 (0–135)	45.8 ± 47.8 (0–200)	0.521
Perianal disease at diagnosis, n (%)	6 (33.3)	10 (28.6)	3 (11.5)	6 (17.1)	0.224
Development of perianal disease after diagnosis, n (%)	3 (16.7)	6 (17.1)	5 (19.2)	10 (28.6)	0.636
Concomitant stricturing disease, n (%)	10 (55.6)	23 (65.7)	20 (76.9)	29 (82.9)	0.142
Leukocyte count (10^3/μL)*	9.08 ± 2.76 (5.75–15.00)	10.16 ± 4.32 (4.30–21.80)	9.41 ± 2.96 (5.30–15.60)	9.90 ± 3.11 (5.20–16.37)	0.871
Hemoglobin (g/dL)*	11.1 ± 1.7 (8.5–14)	11.3±2.8 (8.3–14.8)	11.4 ± 1.4 (8.5–14.2)	11.7 ± 1.6 (8.6–14.3)	0.699
CRP (mg/L)[Δ]	59.3 ± 87 (8.7–318)	38.6±40.3 (1.2–157)	96.6 ± 104 (1.4–257.8)	55 ± 66.7 (4.4–247.7)	0.786
Albumin (g/dL)[Π]	3.5 ± 0.6 (2.3–4.4)	3.4±0.6 (2.4–4.4)	3.7 ± 0.7 (2–4.8)	3.3 ± 0.497 (2.5–4.2)	0.478
Colonoscopic findings, n (%)[•]					
Aphthous ulcers	3 (16.7)	5 (14.3)	2 (8)	10 (28.6)	0.212
Linear ulcers	2 (11.1)	4 (11.4)	1 (4)	7 (20)	0.344
Deep ulcers	3 (16.7)	1 (2.9)	0 (0)	2 (5.7)	0.123
Stricture	7 (38.9)	12 (34.3)	6 (24)	15 (42.9)	0.496
Fistula opening	0 (0)	3 (8.6)	1 (4)	0 (0)	0.227
Bowel resection performed, n (%)	5 (27.8)	10 (28.6)	20 (76.9)	23 (65.7)	**<0.001**
Diverting ostomy performed, n (%)	3 (16.7)	6 (17.1)	1 (3.8)	13 (37.1)	**0.012**
Permanent ostomy, n (%)	1 (5.6)	1 (2.9)	1 (3.8)	5 (14.3)	0.314
Organ-preserving surgery, n (%)	0 (0.0)	5 (14.3)	7 (26.9)	4 (11.4)	0.088
Recurrent intervention-unrelated penetrating events, n (%)	0 (0.0)	1 (2.9)	1 (3.8)	17 (48.6)	**<0.001**
Recurrent intervention-related penetrating events, n (%)	1 (5.6)	1 (2.9)	3 (11.5)	24 (68.6)	**<0.001**

*Leukocyte count and hemoglobin values were available for 11 of 18, 21 of 35, 12 of 26, and 18 of 35 patients in groups 1–4, respectively. [Δ]CRP values were available in 11/18, 19/35, 11/26, and 18/35 patients in groups 1–4, respectively. Values for [Π]-albumin were available in 10 of 18, 15 of 35, 10 of 26, and 13 of 35 patients in groups 1–4, respectively. [•]Endoscopic data were unavailable in one patient; analyses were based on 113 patients. Results are presented as mean ± standard deviation (range) or n (%), as appropriate. Statistically significant p-values (p < 0.05) are shown in bold. CD, Crohn's disease; CRP, C-reactive protein; GI, gastrointestinal; IBD, inflammatory bowel disease.

groups (p = 0.314). Organ-preserving surgical procedures were more frequently performed in the abscess-associated fistula group (26.9; n = 7), although this difference did not reach statistical significance (p = 0.088). Recurrent penetrating complications were evaluated separately as intervention-related and intervention-unrelated events. The rate of recurrence without interventional procedures was significantly higher in the overlapping group–other subgroup (48.6%, n = 17) than in the IA, IF, and abscess-associated fistula groups (p < 0.001). Similarly, recurrence following interventional procedures was most frequent in the overlapping group–other subgroup (68.6%, n = 24), and this rate was significantly higher than that in the other three groups (p < 0.001).

Factors Associated with Abscess Size and Surgical Outcomes in Patients with Abscess Complications

Among the 44 patients in the IA and abscess-associated fistula groups, abscess size data were available for 34 patients and were included in the analysis (Table 3). No significant associations were observed between abscess size and patient age, age at CD diagnosis, interval to abscess development, smoking duration, baseline CRP, hemoglobin, or albumin levels (all p > 0.05). In contrast, abscess size showed a significant positive correlation with disease duration (r = 0.384, p = 0.025) and with baseline leukocyte count (r = 0.535, p = 0.022). In addition, the mean abscess size was significantly larger in patients with a history of corticosteroid use than in those without prior corticosteroid exposure (5 ± 2.8 cm vs. 3.4 ± 1.8 cm, p = 0.05). Risk factors

Table 3. Factors associated with abscess size in patients with abscess complications.

Continuous variables (correlation analysis)	r	p-value
Disease duration (months)	0.384	0.025
Time to abscess development (months)	0.314	0.071
Age (years)	0.136	0.443
Age at diagnosis (years)	-0.067	0.706
Baseline leukocyte (10^3/μL)*	0.535	0.022
Baseline CRP (mg/L)$^{\Delta}$	0.194	0.456
Baseline hemoglobin (g/dL)*	-0.299	0.228
Baseline albumin (g/dL)$^{\Pi}$	-0.412	0.112
Categorical variables (group comparisons)	**Abscess size (cm)**	**p-value**
Sex Female Male	 3.5 ± 2.2 3.9 ± 2	0.457
Smoking status Never smoker Former smoker Current smoker	 3.8 ± 2 3.3 ± 2 4.2 ± 2.3	0.533
Disease location at diagnosis (Montréal) Ileal (L1) Colonic (L2) Ileocolonic (L3)	 3.3 ± 2.3 4.1 ± 2 3.9 ± 1.9	0.694
Perianal disease at diagnosis	3.4 ± 0.4	0.647
AZA use ⩽3 months	4.6 ± 2.9	0.539
CS use ⩽3 months	4.7 ± 2.3	0.163
Past AZA use	3.5 ± 1.6	0.969
Past CS use	5 ± 2.8	**0.05**

*Leukocyte and hemoglobin values were calculated based on available data from 18 patients. $^{\Delta}$CRP values were calculated based on available data from 17 patients. $^{\Pi}$Albumin values were calculated based on available data from 16 patients. Results are presented as mean ± standard deviation or as correlation coefficient (r), as appropriate. AZA, azathioprine; CRP, C-reactive protein; CS, corticosteroid.

for surgical intervention were further evaluated in the combined abscess cohort. In univariate analyses, no variable other than abscess size was significantly associated with the need for surgery. Active smoking status and corticosteroid use, whether within three months before abscess diagnosis or in the past, were not significantly associated with surgical risk (all $p > 0.05$). In multivariable logistic regression analysis, abscess size and the presence of multiple abscesses emerged as independent predictors of surgery. Each 1-cm increase in abscess size was associated with a 1.92-fold higher risk of surgical intervention ($p = 0.034$), and patients with multiple abscesses had a markedly higher risk of surgical intervention compared with those with a single abscess (OR = 16.02, $p = 0.042$). To further evaluate the discriminative ability of abscess size in predicting the need for surgical intervention, ROC curve analysis was performed. The optimal cut-off value for abscess size was identified as 2.75 cm based on the Youden index (0.393). The AUC was 0.721 ($p = 0.029$), indicating acceptable discriminatory performance. At this threshold, abscess size predicted the need for surgical intervention with a sensitivity of 86.7% and a specificity of 52.6%.

Discussion

In this study of patients with CD complicated by non-perianal penetrating manifestations, we comprehensively characterized the spectrum, management, and outcomes of penetrating complications at a large tertiary referral center. Our findings demonstrate that penetrating complications frequently develop during the disease course and are associated with substantial morbidity. Patients with combined abscess and fistula phenotypes exhibited a distinctly worse clinical course, with higher rates of bowel resection and recurrent penetrating events compared with those with an IA or an IF. In fistulizing disease, the presence of concomitant strictures—particularly in segments different from the fistula—emerged as a strong independent predictor of surgical intervention. Moreover, in patients with

abscess complications, larger and multiple abscesses were independently associated with the need for surgery; an abscess diameter of 2.75 cm provided a clinically relevant threshold for predicting that need. Collectively, these findings highlight key phenotypic features that may help identify high-risk patients and inform timely, individualized management strategies in non-perianal penetrating CD.

Population-based cohorts suggest that penetrating complications at diagnosis are relatively uncommon. Thia et al. (8) reported that 14% of 306 patients from Olmsted County, Minnesota had penetrating complications at diagnosis. In contrast, 26.3% of patients in our cohort already had penetrating complications at diagnosis, while the majority developed them during follow-up, reflecting both the dynamic evolution of disease behavior and the enrichment for severe phenotypes in a tertiary referral setting. Penetrating intestinal CD has been reported in approximately 16% of patients (15). In line with this, IAs accounted for 15.7% of cases in our study. However, we observed a substantial burden of fistulizing disease and a high frequency of combined abscess–fistula presentations, consistent with prior observations that fistulas often arise in association with adjacent inflammatory masses or abscesses (17).

Because postoperative intra-abdominal abscesses and enterocutaneous fistulas are recognized septic complications (18), careful differentiation between spontaneous penetrating disease and iatrogenic events is essential. To minimize confounding, we excluded patients whose penetrating complications followed intra-abdominal surgery or radiological intervention. Furthermore, among patients with both abscess and fistula, we defined the abscess-associated fistula subgroup as those who developed fistulas within three months of abscess diagnosis without any intervention. This approach allowed a pathophysiologically more homogeneous evaluation of spontaneous penetrating behavior and revealed that this subgroup carried a distinctly worse prognosis.

Disease location has been associated with complicated CD in several cohorts, with ileal involvement frequently reported among patients with penetrating disease (19,20). In our data, ileal involvement was more frequent in patients with IA than in those with IF, supporting a potential anatomical predisposition to abscess formation. Conversely, when comparing all four phenotypic groups, colonic involvement was more common in the IF group than in the overlapping group (other subgroup), suggesting that distinct anatomical distributions may contribute to different presentations of penetrating disease.

A persistent challenge in CD classification is the dynamic nature of disease behavior, with stricturing and penetrating phenotypes often evolving together over time (6). In a large multicenter study, Fan et al. (21) demonstrated that a substantial subset of patients ultimately develop both stricturing and penetrating complications, supporting the concept of a mixed phenotype. In our cohort, obstructive segments were common prior to or at the time of penetrating complications. Although stricture prevalence did not differ significantly among the four penetrating phenotypic groups, strictures were highly prognostically informative in fistulizing disease: their presence, particularly in segments distinct from the fistula, was independently associated with markedly increased surgical risk. This finding reinforces the central role of structural damage in guiding surgical decision-making and aligns with prior observations linking luminal narrowing to penetrating complications (22,23).

The relationship between intestinal fistulization and perianal disease remains debated. Tang et al. (24) reported a strong association between perianal and intestinal fistulas, whereas others have suggested that these may represent distinct clinical phenotypes (25). In our cohort, perianal disease at diagnosis was present in 21.9% of patients with penetrating complications, but this prevalence did not differ across phenotypic groups. However, the retrospective design and limited longitudinal data precluded a more definitive assessment of the temporal and causal relationship between perianal disease and intestinal penetrating complications.

Non-perianal intestinal fistulas occur in approximately 10–15% of CD patients, most commonly as enterocolic and enteroenteric fistulas (15). In our study, enterocolic fistulas were the most frequent subtype, consistent with prior reports. Evidence supporting medical therapy for fistulizing disease is largely derived from perianal cohorts, and intestinal fistulas are known to respond less favorably to anti-TNF therapy (12,26,27). Consistent with this, 40% of patients in our IF group ultimately required surgery despite frequent initiation or escalation of anti-TNF treatment. This finding supports the prevailing view that intestinal fistulas often necessitate surgical management (14,28). Notably, in our analyses, stricturing disease—rather than immunosuppressive exposure—was the dominant determinant of surgical risk, consistent with reports identifying strictures as key drivers of the need for surgery (23).

Intra-abdominal abscesses are frequent penetrating complications, reported in up to 30% of patients during the disease course (17). In our cohort, abscesses were most commonly localized to the ileocecal region, consistent with prior studies of spontaneous abscesses and phlegmon (13,29). The mean abscess size was comparable to values reported in other cohorts (30,31). Abscess size has direct implications for management: ECCO guidance cautions

against immunosuppression in large abscesses and notes the limited efficacy of antibiotics alone in some cases (32), while previous studies suggest that abscesses larger than 3–4 cm are more likely to require drainage or surgery (12,29,33). In our study, ROC analysis identified 2.75 cm as a practical threshold for predicting surgical need, with high sensitivity but moderate specificity. Furthermore, abscess size and multiplicity independently predicted surgical intervention, underscoring that abscess burden and morphology are central determinants of outcome. The association between prior corticosteroid exposure and larger abscess size observed in our cohort may reflect a more extensive inflammatory burden, although causality cannot be inferred.

Although predictors of developing penetrating CD are relatively well described, fewer data address the prognosis after penetrating complications have occurred (7,34). Prior studies have shown that penetrating behavior is associated with worse postoperative outcomes than inflammatory or stricturing phenotypes (35) and that the presence of abscesses increases the need for surgery in ileal penetrating disease (19). Consistent with this, we observed significantly higher bowel resection rates and recurrence rates of penetrating complications—both those unrelated to interventions and those occurring after radiologic or surgical procedures—in patients with combined phenotypes, particularly in the abscess-associated fistula and overlapping group–other subgroups. These findings emphasize that combined penetrating presentations represent a particularly high-risk subgroup requiring close surveillance and timely multidisciplinary management.

Study Limitations

The strengths of this study include the large cohort from a long-standing tertiary referral center, the extended observation period, and the detailed phenotypic characterization of non-perianal penetrating CD. Exclusion of postoperative and intervention-related cases and the subclassification of abscess-associated fistulas enabled a more homogeneous assessment of spontaneous penetrating behavior. The use of multivariable analyses and ROC methodology allowed identification of independent predictors of surgical risk and yielded a clinically applicable abscess size threshold. Several limitations should be acknowledged. The retrospective, single-center design may limit causal inference and generalizability, and may introduce referral bias toward more severe disease. A substantial proportion of patients were excluded based on predefined criteria to minimize iatrogenic confounding, which may have introduced selection bias. In addition, relatively small subgroup sizes may have limited the power of some comparisons, and incomplete longitudinal data onperianal disease activity and disease severity constrained more-detailed phenotypic analyses.

Conclusion

In conclusion, non-perianal penetrating CD represents a heterogeneous but clinically aggressive phenotype that develops during follow-up and is associated with substantial morbidity. Patients with combined abscess and fistula presentations experience the poorest outcomes, with higher rates of bowel resection and recurrent penetrating events, underscoring the need for close surveillance and multidisciplinary management in this subgroup. Concomitant strictures—when located in segments different from the fistula—emerge as the strongest determinants of surgical need in fistulizing disease, highlighting the pivotal role of structural damage in guiding therapeutic decisions. In patients with abscess complications, abscess size and multiplicity are key drivers of surgical risk, and an abscess diameter of 2.75 cm may serve as a practical threshold to identify patients unlikely to respond to conservative management. These findings emphasize the importance of detailed phenotypic assessment beyond traditional classifications and support an individualized, risk-adapted approach to the management of penetrating CD. Prospective multicenter studies incorporating standardized imaging and phenotyping are warranted to validate these observations and refine treatment algorithms for this challenging population.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (approval number: 189, approval date: 31.05.2022).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: A.P., T.E., Concept: O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Design: O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Data Collection or Processing: A.P., O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Analysis or Interpretation: O.K.B., Ö.P., A.F.Ç., A.İ.H., Literature Search: A.P., Ö.P., Writing: A.P., O.K.B.

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