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Analysis of Risk Factors for Anorectal Stenosis of Perianal Fistulizing Crohn's Disease

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Background: To analyze the risk factors of anorectal stenosis associated with perianal fistulizing Crohn's disease (PFCD).

Material/Methods: We retrospectively analyzed 139 cases of PFCD from January 2010 to December 2017 at the Affiliated Hospital of Nanjing University of Chinese Medicine. They were divided into 2 groups according to whether anorectal stenosis occurred. The possible factors associated with anorectal stenosis of PFCD were selected based on the literature review and clinical observations. Univariate analysis was performed to screen the risk factors of anorectal stenosis, and multivariate logistic regression analysis was performed on these risk factors and factors that were clinically considered to be potentially influential, to screen out the independent risk factors of anorectal stenosis.

Results: We found that 44 cases (31.7%) of PFCD were associated with anorectal stenosis. Univariate analysis showed that CDAI, lesion location, and age at diagnosis were risk factors for anorectal stenosis of PFCD. Logistic regression analysis showed that mild (fair to good) (OR=3.833, 95% CI: 1.123~13.080) to moderate (poor) (OR=7.345, 95% CI: 1.964~27.474) CDAI and age at diagnosis (OR=1.067, 95% CI: 1.013~1.124) were independent risk factors for anorectal stenosis of PFCD.

Conclusions: Higher CDAI and older age at diagnosis appear to confer higher risk of anorectal stenosis associated with PFCD.

MeSH Keywords: Behavioral Risk Factor Surveillance System • Crohn Disease • Fistula

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Background

Anal fistula is the most common perianal Crohn's disease (CD); about 35% of CD patients are complicated with anal fistula [1], and it is the initial symptom in 5% of CD patients [2]. We analyzed the data on perianal fistulizing Crohn's disease (PFCD) from January 2010 to December 2017 in the Department of Colorectal Surgery, Affiliated Hospital of Nanjing University of Chinese Medicine (AHNUCM), and found that among 139 PFCD cases, 44 cases (31.7%) were complicated with anorectal stenosis, which exceeded the incidence rates of other complicated perianal lesions (such as verrucous dermatophytes, anal fissure, abscess and rectovaginal fistula) [3]. There is an abundance of literature on PFCD, but data on other types of perianal CD remain scarce. The epidemiological investigation of anorectal stricture in CD has not been reported. Fibrotic anorectal stricture in CD usually occurs as a result of chronic inflammation and often occurs late in the course of the disease [4]. Anorectal stenosis affects defecation functions, and even requires fecal diversion in severe cases. It has a severe impact on patients' daily life. In an attempt to minimize the incidence of anorectal stenosis of PFCD, we analyzed the clinical data of 139 cases to identify potential influencing factors.

Material and Methods

Data collection

In our research center, specialized Inflammatory Bowel Disease medical staff registered basic information such as sex, age, body mass index (BMI), asked for medical history such as CD course, anal fistula course, clinical symptoms, abdominal surgery history, perianal surgery history, and medication history, and performed examinations such as endoscopy, imaging, and laboratory tests of patients with PFCD who were hospitalized. These medical staff were trained to evaluate the patients according to the diagnostic criteria, clinical evaluation, and classification criteria. We recorded data on Montreal classification, anal fistula type, number of external openings, concomitant perianal lesions, CD activity index (CDAI), perianal disease activity index (PDAI) and some laboratory indexes.

We retrospectively analyzed the data of 139 cases of PFCD, who were hospitalized for the first time at the Department of Colorectal Surgery of AHNUCM from January 2010 to January 2017. The clinical information is shown in Table 1. The patients were divided into 2 groups according to whether anorectal stenosis occurred, and then statistical analysis was conducted. This study conformed to the Helsinki Declaration and we obtained informed consent from all patients. The study was approved by the Ethics Committee of AHNUCM (approval number of 2017NL-071-02).

Diagnostic criteria

The diagnostic criteria for PFCD referred to "A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulizing Crohn's disease" published in 2014 by the World Gastroenterology Organization [5]. The diagnostic criteria of anorectal stenosis referred to "diagnostic basis, syndrome classification, and efficacy evaluation of anorectal stenosis" in "Criteria for the diagnosis and treatment of diseases and syndromes in internal medicine of traditional Chinese medicine" (ZY/T001.1-94), which is the Chinese medicine industry standard of the People's Republic of China [6]. Anorectal stenosis referred to the narrowing of the anal and rectal passages caused by any reason and leading to defecation difficulties. It was diagnosed based on difficult defecation, a history of perianal inflammation, anal injury or anorectal surgery, and index finger difficulty on examination.

Clinical evaluation and classification criteria

The nutritional status of the patients was assessed by BMI [7], with 18.5~23.9 as normal and <18.5 and ≥24 as abnormal. The classification of CD was conducted using the Montreal Phenotypic Classification proposed by the World Gastroenterology Working Group in 2005 [8], which includes age (A), lesion site (L), and disease behavior (B). In this study, B2 type included anorectal stenosis, and B3 type excluded the penetration caused by anal fistula. The Best CDAI algorithm [9] was used to evaluate the activity index of CD: <150 points, very well;150~220 points, fair to good; 221~450 points, poor; >450, very poor. PDAI was used to evaluate the activity of PFCD [10]: ≤4 indicating remission stage and >4 indicating active stage. Classification of anal fistulas referred to the American Gastroenterological Association's medical position statement about perianal Crohn's disease in 2003 [11], and divided into simple anal fistula and complex anal fistula. Simple anal fistula refers to a low (superficial fistula, low inter-sphincteric or trans-sphincter fistula), single, external opening, with no abscess signs such as pain or fluctuation, no rectovaginal fistula, and no anorectal stenosis, whereas complex anal fistula refers to the opposite.

Statistical analysis

SPSS 23.0 software was used for statistical analysis. The group chi-square test and likelihood ratio test were used for enumeration data. Unconditional logistic regression analysis was used for multiple factor analysis. The test level was α=0.05.

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Table 1. Patient characteristics.

Item	N (%)	Item	N (%)
Sex		Number of external openings	
Male	107 (77.0)	1	48 (34.5)
Female	32 (23.0)	2	44 (31.7)
BMI (kg/m^2)		≥3	47 (33.8)
<18.5	63 (45.3)	Concomitant perianal diseases	
18.5~23.9	64 (46.0)	Anorectal stenosis	44 (31.7)
≥24	12 (8.7)	Fissure	6 (4.3)
previous abdominal surgery (no. of times)		Abscess	33 (23.7)
1	23 (16.5)	Rectovaginal fistula	7 (5.0)
>1	4 (2.9)	Verrucous skin	43 (30.9)
History of perianal surgery		Diagnostic age (years)	
Anal fistula surgery	38 (27.3)	≤16 (A1)	6 (4.3)
Perianal abscess surgery	56 (40.3)	17~40 (A2)	119 (85.6)
Hemorrhoids surgery	6 (4.3)	>40 (A3)	14 (10.0)
Anal fissure surgery	2 (1.4)	Location of lesion	
Excision of perianal masses	1 (0.7)	Ileum (L1)	33 (23.7)
Previous perianal surgery (no. of times)		Colon (L2)	37 (26.6)
1	58 (41.7)	Ileocolon (L3)	69 (49.6)
>1	32 (23.0)	Disease behavior	
Medication history		Nonstricturing nonpenetrating (B1)	72 (51.8)
5-ASA	62 (44.6)	Stricturing (B2)	57 (41.0)
SASP	15 (10.8)	Stricturing and penetrating (B2B3)	10 (7.2)
Immunosuppressor	24 (17.3)	CDAI	
Corticosteroid	31 (22.3)	Very well (<150 points)	49 (35.3)
Biologics	22 (15.8)	Fair to good (150~220 points)	53 (38.1)
Antibiotic	16 (11.5)	Poor (221~450 points)	37 (26.6)
Enteral nutrition	28 (20.1)	Very poor (>450 points)	0 (0)
Elsea	23 (16.5)	PDAI	
None	37 (26.6)	Remission stage (≤4 points)	8 (5.6)
CD course (year)		Active stage (>4 points)	131 (94.2)
<1	78 (56.1)	CRP (mg/L)	
1~5	42 (30.2)	<8	86 (61.9)
>5	19 (13.7)	≥8	53 (38.1)

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Table 1 cotntinued. Patient characteristics.

Item	N (%)	Item	N (%)
Anal fistula course (year)		ESR (mm/h)	
<1	74 (53.2)	Above normal	74 (53.2)
1~5	50 (36.0)	Normal	65 (46.8)
>5	15 (10.8)	Hb (g/L)	
Relationship between the 2 courses		Below normal	54 (38.8)
Anal fistula appeared first	66(47.5%)	Normal	85 (61.2)
Simultaneous	27(19.4%)	PLT (×10^9/L)	
Intestinal inflammation appeared first	46(33.1%)	<100	1 (0.7)
Clinical symptoms		100~300	88 (63.3)
Diarrhea	64 (46.0)	≥300	50 (36.0)
Perianal symptoms only	41 (29.5)	WBC (×10^9/L)	
Loss of weight	37 (26.6)	<4	11 (7.9)
Abdominal pain	30 (21.6)	4~10	115 (82.7)
Fever	27 (19.4)	>10	13 (9.4)
Hematochezia	23 (16.5)	Alb (g/L)	
Anemia	21 (15.1)	<35	33 (23.7)
Anal fistula type		35~50	103 (74.1)
Simple	13 (9.4)	>50	3 (2.2)
Complex	126 (90.6)		

CDAI – CD activity index; PDAI – perianal disease activity index; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; WBC – leukocyte, PLT – platelet; HB – hemoglobin; Alb – albumin. a: Refers to treatment with Chinese herbal medicine, extract of Chinese herbal medicine, transplantation of fecal bacteria, anti-tuberculosis, and antiviral treatment.

Results

Univariate analysis

Patients were divided into 2 groups according to whether accompanied anorectal stenosis occurred, and all variables that might cause anorectal stenosis on the basis of literatures review and clinical observation were analyzed. Univariate analysis was conducted on these clinical data to screen out the factors influencing anorectal stenosis of PFCD. Since we classified anorectal stenosis into B2, which was related to disease behavior, we did not include disease behavior into the univariate analysis objects. Univariate analysis results showed that CDAI (p<0.001), lesion location (p=0.019), and age at diagnosis (p=0.037) are risk factors for anorectal stenosis of PFCD, while CRP level, sex, number of external openings, BMI, PDAI status, corticosteroid usage, previous medication, biologics therapy history, combination therapy history, previous perianal surgery history, previous abdominal surgery history, anal fistula course and CD course were unrelated (p>0.05) (Table 2).

Multivariate logistic regression

Multivariate logistic regression analysis was conducted on the risk factors detailed above and variables that were clinically considered to be potentially influential to determine the independent risk factors of anorectal stenosis of PFCD. The results showed that mild (fair to good) (OR=3.833, 95% CI: 1.123~13.080) to moderate (poor) (OR=7.345, 95% CI: 1.964~27.474) CDAI and age at diagnosis (OR=1.067, 95% CI: 1.013~1.124) were independent risk factors for anorectal stenosis of PFCD (Table 3).

Treatment of patients with anorectal stenosis

We found that 86.4% (38 patients) of these anorectal stenosis patients received medication prior to the diagnosis of

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Table 2. Univariate analysis of anorectal stenosis of PFCD.

Clinical features	Total N	Without anorectal stenosis N=95	With anorectal stenosis N=44	χ^2 value	P value
CRP (mg/l)				1.087	0.297
<8	53	39 (73.6)	14 (26.4)		
≥8	86	56 (65.1)	30 (34.9)		
Sex				0.239	0.625
Male	107	72 (70.6)	35 (32.7)		
Female	32	23 (67.3)	9 (28.1)		
External opening number				1.546	0.462
1	48	36 (75.0)	12 (25.0)		
2	44	29 (65.9)	15 (34.1)		
≥3	47	30 (63.8)	17 (36.2)		
BMI (kg/m^2)				2.946*	0.244
18.5~23.9	64	46 (71.9)	18 (28.1)		
<18.5	63	39 (61.9)	24 (38.1)		
≥24.0	12	10 (83.3)	2 (16.7)		
CDAI				19.433	<0.001
Very well	49	44 (89.8)	5 (10.2)		
Fair to good	53	34 (64.2)	19 (35.8)		
Poor	37	17 (45.9)	20 (54.1)		
PDAI				1.683*	0.195
Remission stage	8	7 (87.5)	1 (12.5)		
Active stage	131	88 (67.2)	43 (32.8)		
Previous perianal surgery				0.038	0.845
Yes	49	34 (69.4)	15 (30.6)		
No	90	61 (67.8)	29 (32.2)		
Previous abdominal surgery				2.034	0.154
Yes	111	79 (71.2)	32 (28.8)		
No	28	16 (57.1)	12 (42.9)		
Anal fistula course (year)				3.994	0.136
<1	74	54 (73.0)	20 (27.0)		
1–5	50	34 (68.0)	16 (32.0)		
>5	15	7 (46.7)	8 (53.3)		
CD course (year)				4.893	0.087
<1	78	59 (75.6)	19 (24.4)		
1–5	42	26 (61.9)	16 (38.1)		
>5	19	10 (52.6)	9 (47.4)		

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Table 2 continued. Univariate analysis of anorectal stenosis of PFCD.

Clinical features	Total N	Without anorectal stenosis N=95	With anorectal stenosis N=44	χ^2 value	P value
Location of lesion				7.935	0.019
L1	33	27 (81.8)	6 (18.2)		
L2	37	19 (51.4)	18 (48.6)		
L3	69	49 (71.0)	20 (29.0)		
Age at diagnosis				6.609*	0.037
A1	6	6 (100)	0 (0)		
A2	119	82 (68.9)	37 (31.1)		
A3	14	7 (50.0)	7 (50.0)		
Previous medication				3.780	0.052
Yes	102	65 (63.7)	37 (36.3)		
No	37	30 (81.1)	7 (18.9)		
Previous corticosteroid therapy				0.007	0.935
Yes	31	21 (67.7)	10 (32.3)		
No	108	74 (68.5)	34 (31.5)		
Previous biologics therapy				2.193	0.139
Yes	22	18 (81.8)	4 (18.2)		
No	117	77 (65.8)	40 (34.2)		
Previous combination therapy				1.038	0.308
Yes	67	43 (64.2)	24 (35.8)		
No	72	52 (72.2)	20 (27.8)		

* Likelihood ratio test.

anorectal stenosis, and 4 of them had received biologic therapy previously (Table 2). After the diagnosis of anorectal stenosis, these patients received anal dilatation or medication according to the component of the stenosis; 80% of them received dilatation under anesthesia because of fibrotic stenosis, and the others received a biologic agent or immunosuppressor because of inflammatory stenosis.

Discussion

Perianal CD and location of intestinal lesion

The incidence of perianal CD is closely related to the location of intestinal lesions, and it is significantly increased when inflammation involves the rectum [12,13]. Anal fistula is associated with 12% of isolated ileal CD, 15% of ileal colon CD, 41% of colon CD when the rectum is not involved, and 92% of colon CD when the rectum is involved, and only 5% CD patients initially present with an anal fistula without any intestinal inflammation [14,15]. Although the European Crohn's and Colitis Organization (ECCO) Consensus did not elaborate on the relationship between anorectal stenosis occurrence and intestinal inflammation location, our study showed that the anorectal stenosis incidence rate of colonic CD (48.6%) was higher than of ileac CD (18.2%) and ileocolic CD (29.0%), and the difference was statistically significant (P=0.019). Therefore, we speculated that incidence of anal fistula and anal anorectal stenosis of CD was correlated with distal intestinal lesions.

The development of CD itself can lead to damage to the internal and external sphincter and perineal body, and proctitis leads to decreased rectal compliance. Even a moderate level of sphincter function decline can eventually result in incontinence due to decreased colonic absorption of water, rectal capacity, and compliance. The only surgical method for anal

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Table 3. Multivariate logistic regression analysis of anorectal stenosis of PFCD.

Item	B value	Wald χ^2 value	df	P value	OR value	95% CI	
						Lower limit	Upper limit
Location of lesion		2.073	2	0.361			
L2	0.477	0.482	1	0.487	1.612	0.419	6.197
L3	–0.225	0.130	1	0.719	0.799	0.234	2.719
CD course (years)		0.235	2	0.889			
1–5	0.002	0.000	1	0.997	0.998	0.356	2.797
>5	–0.295	0.188	1	0.665	0.745	0.196	2.827
CDAI		8.781	2	0.012			
Fair to good	1.344	4.602	1	0.032	3.833	1.123	13.080
Poor	1.994	8.777	1	0.003	7.345	1.964	27.474
Diagnostic age	0.065	5.979	1	0.014	1.067	1.013	1.124
CRP (≥8 mg/l)	0.226	0.229	1	0.632	1.253	0.497	3.160
PDAI	0.052	0.495	1	0.482	1.053	0.912	1.216
Previous medication (yes)	0.635	1.000	1	0.317	1.887	0.543	6.555
Constant	–4.955	15.897	1	0.000	0.007		

Age at diagnosis and PDAI were included as continuous variables.

fistula of CD complicated with proctitis is seton drainage, and deterministic surgical methods to promote fistula closure are not feasible [5]. When the anorectal stenosis is associated with proctitis, anal dilatation often leads to inflammation tissue bleeding, so medical treatment to control proctitis should be the first choice. Anal dilatation and sternotomy are more suitable for patients with fibrous stenosis. If the stenosis is extensive, it is difficult for patients to avoid bypass surgeries.

Anal fistula, anorectal stenosis, and intestinal inflammatory activity in CD

Previous studies showed that the risk factors of perianal lesions in CD are related not only to lesion location [16–18], but also to sex, age, and race. However, no correlation between the incidence of CD perianal lesions and intestinal inflammatory activity has been reported. The results of the present study suggest that higher CDAI is associated with higher the risk of anorectal stenosis, meaning that the severity of intestinal inflammation of CD can directly affect the incidence of rectal stenosis. Most CD patients are initially diagnosed on the basis of pathological changes in inflammation. When diagnosed, only one-third of patients have evidence of stenosis or penetration. After chronic relapses, the inflammatory disease phenotype tends to shift to a stenosis and/or penetrating phenotype, characterized by serious complications such as stenosis or fistula. Epithelial mesenchymal transformation (EMT) is involved in tissue healing in response to traumas. When a tissue or organ is injured, it triggers a complex chain of healing reactions. This delicate process of tissue repair is important for stability of the internal environment of organs. However, the imbalance between excessive and inadequate tissue repair can impair organ function, with ulceration and fistula formation on the one hand, and fibrosis and stenosis on the other [19]. EMT seems to be the driving force for the development of fistulas and the key to the development of fibrosis [20,21]. In this study, 31.7% of PFCD patients were complicated with rectal stenosis, more than with other complications, which confirms the theory that the mechanisms of development of anal fistula and fibrosis are similar. There is evidence showing that intestinal inflammation is the main driver of CD fibrosis [22,23]. This evidence may also explain our observation that higher CDAI is associated with greater risk of rectal stenosis. In this study, the patients who had previously received medication had higher incidence of rectal stenosis (p=0.052), although the difference was not statistically significant. Why did the medication fail to control inflammation but lead to a higher incidence of stenosis? This may be related to the longer course of CD in these patients; 74 of the 102 patients who had previous medication had a CD course of more than 1 year. Inflammatory or fibrous stenosis can develop due to long-term inflammation under inappropriate medication.

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Age and anorectal stenosis in CD

Cosnes et al. [18] reported that CD patients under the age of 40 years had a higher incidence of perianal lesions, but this study showed that the incidence of anorectal stenosis increased by 6.1% for each additional year of age, meaning that older age is associated with higher incidence of anorectal stenosis, which is inconsistent with the data we found in our literature review. The reason may be that the age of patients in this group was age at diagnosis. The experience and proficiency of physicians prescribing CD treatment can enormously affect the time span from onset to diagnosis. A longer course of disease could mean older age at diagnosis and longer development of inflammation, and longer development of inflammation can lead to increased incidence of perianal lesions. In this group, the incidence of anorectal stenosis of patients with a disease course longer than 5 years was 47.4%, which is higher than the 38.1% of patients with 1–5 years and the 24.4% of patients with less than 1 year. Although the difference was not statistically significant, the influence of course of disease on the incidence of anorectal stenosis can be preliminarily speculated.

Conclusions

In conclusion, the lesion location, degree of intestinal inflammation, and age at diagnosis of CD patients all affect the occurrence of anorectal stenosis. Especially, the degree of intestinal inflammation and age at diagnosis are independent risk factors for the occurrence of anorectal stenosis. Our findings suggest that higher CDAI and older age at diagnosis are associated with higher risks of anorectal stenosis associated with PFCD. For medical personnel, it is important to choose personalized therapeutic plans, control the intestinal inflammatory activity of patients, and achieve early diagnosis and early treatment to prevent the occurrence of anorectal stenosis. In future research, we plan to assess the long-term outcomes of anorectal stenosis to determine what factors influenced the outcome.

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