

## Original Article

# Etiologic and clinical analysis of chronic complex anal and rectal inflammation in children less than 3 years old

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**Abstract:** Objective: To analyze the etiology and clinical diagnostic method for chronic complex anal and rectal inflammation in children less than 3 years old. Method: Seven children (5 males and 2 females; 1 year 8 months to 3 years of age at the time of physician evaluation) with chronic complex anal and rectal inflammation were enrolled between May 2008 and May 2013 at our hospital. Clinical history, results of auxiliary examinations, and empirical treatment of the children were analyzed retrospectively combined with the etiologic diagnosis. Results: Four patients were confirmed to have Crohn's disease and one patient was confirmed to have intestinal tuberculosis; two patients were suspected to have Crohn's disease. Anemia and low pre-albumin level were common (seven patients); serologic testing revealed four patients with elevated IgG levels and seven patients with elevated IgA levels; there were no patients with positive tuberculosis antibody titers and two patients were weakly positive for C-ANCA (one patient with Crohn's disease and one patient intestinal tuberculosis). Colonoscopies revealed that the entire colon was affected in one patient, the left hemicolon was affected in four patients, and the sigmoid colon and rectum were affected in two patients. Two patients with Crohn's disease and one patient with intestinal tuberculosis were diagnosed by colonoscopies in combination with histopathologic examinations. Two patients with Crohn's disease were confirmed after empirical drug treatment, and two other patients were not definitely diagnosed. Conclusion: The possibility of Crohn's disease or intestinal tuberculosis should be considered in the clinical diagnosis of complex chronic anal and rectal inflammation in younger children. Local surgery is sometimes unnecessary. Empirical drug treatment should be used if necessary.

**Keywords:** Anal infection, rectal infection, anal stenosis, multiple fistulas, younger children

## Introduction

Perianal infection is very common in infancy, but most affected infants can be cured through conservative treatment or abscess incision and drainage. Few infants have single or multiple fistulas if not cured after prolonged treatment; however, these patients can also be cured by local surgery. In clinical practice, there are very few patients with persistent severe anal and rectal infections, or accompanied by anal inflammatory stenosis or multiple fistulas. For such chronic complex anal and rectal inflammation in the younger children, the primary cause of the disease can be easily neglected or misdiagnosed, then leading to the condition persistent or aggravating. Here, "chronic complex anal and rectal inflammation" means per-

sistent severe anal and rectal infections ( $\geq 2$  months), and/or complicated by anal inflammatory stenosis or multiple fistulas. Seven children less than 3 years old who were admitted to our hospital with chronic complex anal and rectal inflammation were retrospectively analyzed herein to enhance clinician awareness of the etiological diagnosis of these diseases, thereby reducing misdiagnosis and inadequate treatment.

## Materials and methods

### Clinical data

Seven patients (5 males and 2 females; 1 year 8 months to 3 years at the time of physician evaluation, averaging 2 years one month) with

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**Table 1.** Clinical histories of seven younger children with chronic complex anal and rectal inflammation

No.	Gender	Age of onset	Age of visiting doctor	Clinical manifestations	Past histories of surgery
1	Male	1 year 3 months	1 year 10 months	Fever (transient) perianal pain	None
2	Male	1 year 1 month	1 year 8 months	Perianal pain anal stenosis	Transverse colostomy
3	Female	6 months	2 years 1 month	Diarrhea, hematochezia fever (transient) perianal pain anal stenosis	None
4	Male	1 year 3 months	2 years 2 months	Perianal pain anal stenosis	None
5	Male	1 year	2 years	Fever (transient) perianal pain	None
6	Female	1 year 6 months	3 years	Perianal pain	None
7	Male	1 year	1 year 10 months	Perianal pain anal stenosis	Transverse colostomy



**Figure 1.** Chronic perianal inflammation complicated by multiple anal fissures.

chronic complex anal and rectal inflammation were admitted to our hospital between May 2008 and May 2013.

All of the patients were given elemental diet appropriate to their age, and not treated with any immunosuppressors before the onset. They were conservatively treated for “repeated perianal infections”, including anti-inflammatory (cephalosporin combined with metronidazole), anti-diarrhoeal (dioctahedral smectite), and diet therapies (constipation diet), for 10 days to 3 weeks in local hospitals before being admitted to our hospital. The persistence lasted for  $\geq 6$  months in all cases. After anti-inflammatory therapy, perianal inflammation was alleviated in all cases, but relapsed within several weeks or months. Two of the seven patients were treated with transverse colostomy at the local hospitals before admission, and the perianal infections of both infants were alleviated to some extent, although intermittent antibiotic treatment were still required.

### Methods

The clinical histories, laboratory test results, and imaging data were analyzed in combination



**Figure 2.** Multiple anal fistulas and anal inflammatory stenosis complicated by perianal skin inflammation and scarring.

with the final etiologic diagnosis. All seven patients underwent colonoscopies, in which the entire colon and terminal ileum were inspected, and 3-6 blocks of intestinal mucosa from the lesions were obtained for biopsies; the colonoscopic observations and histopathologic features were recorded.

### Results

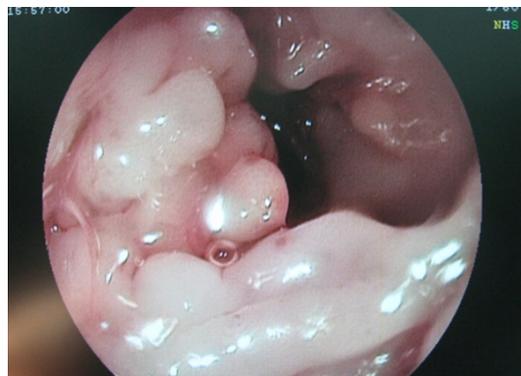
#### *Clinical history analysis (Table 1)*

All of the patients with chronic complex anal and rectal inflammation were Chinese city children and inoculated with BCG vaccination within 24 hours after birth according to the immunization inoculation in China; the patients had no history of exposure to tuberculosis or a family history of chronic inflammatory bowel disease. The ages of onset ranged from 6 months to one year 6 months, averaging one year one month. All of the patients complained of perianal pain without significant abdominal pain. Two patients had persistent diarrhea, one of whom had moderate hematochezia. During the persistence, transient low-grade fevers ( $<38^{\circ}\text{C}$ ) were observed in 3 cases. No apparent abnormalities were appreciated on abdominal palpation. Different degrees of chronic perianal

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**Figure 3.** Erythematous swelling and erosion without ulceration of the intestinal wall was observed under colonoscopy.



**Figure 4.** Multiple areas of polypoid hyperplasia complicated with intestinal stenosis were observed under colonoscopy.

inflammation, combined with multiple anal fissures and fistulas (**Figure 1**), occurred in all of the patients, 4 of whom had anal stenoses (**Figure 2**). The growth and development (according to body height and weight) of all 7 patients were significantly less than normal peers.

### Laboratory tests

All seven patients had co-existing anemia. One patient had symptoms of moderate anemia (hemoglobin: 76 g/L) clinically manifesting as “diarrhea and hematochezia”; the other 6 cases had mild anemia with hemoglobin ranging from 92 g/L to 100 g/L (averaging 94.7 g/L). Of the 7 patients, the peripheral white blood cell counts and C-reactive protein levels at the time of admission were slightly increased (WBC ranging from  $10.8 \times 10^9/L$  to  $13 \times 10^9/L$  and CRP ranging from 12 mg/L to 20 mg/L) in 3. The erythrocyte sedimentation rate (ESR) data were available for 4 patients. The ESR was increased (ranging from 25 mm/h to 40 mm/h) in 3 of 4 patients. With the exception of mild hypoalbuminemia (albumin: 31.2 g/L, RRs 35~55 g/L) in one patient with diarrhea and hematochezia, the albumin levels were within the normal range in all six cases (ranging from 38.1 g/L to 43.3 g/L, averaging 40.5 g/L); however, the pre-albumin levels of all seven cases were lower than normal (ranging from 156 mg/L to 187 mg/L, averaging 175.9 mg/L, RRs 200~400 mg/L).

Immune functions (CD series) were normal in all seven patients; tuberculosis antibody detection, T-spot (tuberculosis infected-T cell spots) detection, and the PPD skin tests were nega-

tive in all patients. The serum IgG levels were increased in 4 patients, IgA levels were increased in 7 patients, and IgM levels were increased in 2 patients. P-ANCA (anti-myeloperoxidase antibodies) were negative in all patients, and C-ANCA (anti-neutrophil cytoplasmic antibodies) were weakly positive in 2 patients.

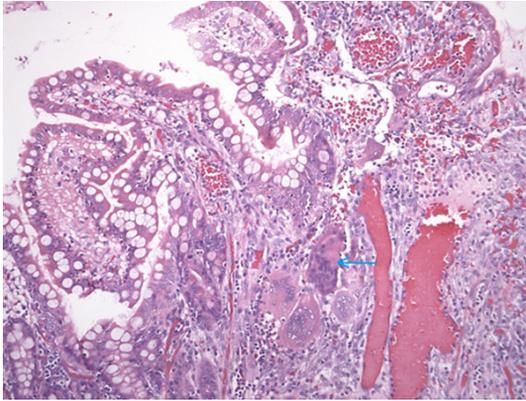
The stool routine test was abnormal in 4 patients; specifically, one patient had 20-30 RBC per HPF (the infant with diarrhea and hematochezia; intestinal amebiasis was excluded using a fecal antigen test), and the other three patients had 6-8 WBC per HPF. The results of stool cultures for all infants were negative.

### Imaging examination

The chest X-ray examinations were normal for all patients. The abdominal and pelvic CT examinations showed asymmetric anal enhancement; obscured perianal adipose tissues suggested perianal inflammatory changes in two patients. No other abnormalities were noted.

### Colonoscopy and histopathologic findings

All seven patients underwent colonoscopies during which the entire colon and terminal ileum were inspected. Under colonoscopy, chronic inflammatory changes of varying degrees in the colonic mucous membranes were observed in all cases. Erythematous swelling and erosion of the intestinal wall without significant ulceration (**Figure 3**) was observed in four patients. Multiple polypoid



**Figure 5.** Inflammatory granulomas were observed under microscopy (blue arrow, HE staining, 10×20).

hyperplasia with intestinal stenosis (**Figure 4**) was observed in three patients. The entire colon was affected in one patient with diarrhea and hematochezia. The left hemicolon was affected in four patients. The sigmoid colon and rectum were affected in two patients. The terminal ileum was not affected in any of the patients.

The pathologic examinations indicated chronic inflammation of the mucous membranes in all seven patients; the histopathologic manifestations of two patients were consistent with Crohn's disease (a moderate amount inflammatory cell infiltration with lymphoid follicles, a moderate number of neutrophils, interstitial edema, a small volume of bleeding, fibroplasia, a small number of eosinophils [approximately 5-12 per HPF], and inflammatory granuloma; (**Figure 5**) and acid-fast bacilli staining was positive in one specimen (diagnosed as intestinal tuberculosis).

### *Diagnosis and treatment (Table 2)*

Colonoscopies combined with histopathologic examinations diagnosed two cases of Crohn's disease, which were treated effectively by drug therapy (glucocorticoids, 2 mg/kg qd); perianal inflammation was completely eliminated and the fistulas closed spontaneously. After maintenance therapy, the cases were followed for 2 and 2.5 years; no recurrences were reported. Of the four patients with clinically-diagnosed Crohn's disease not confirmed by colonoscopy and histopathologic examination, but diagnosed based on perianal disease (existence of complex anal fistulas) and laboratory test

results, two patients were effectively cured using empirical drug therapy (glucocorticoids alone or in combination with metronidazole, 7.5 mg/kg tid). The perianal inflammation was significantly improved. Colonoscopies performed 3 months after empirical drug treatment showed the resolution of mucosal inflammation, and the follow-up 1.5 and 3 years after maintenance therapy revealed no recurrence. Therefore, two patients with Crohn's disease were clinically diagnosed, while one of the other two patients failed to achieve efficacy due to non-compliance with drug treatment. A persistence was reported in this case, and empirical drug treatment is ongoing. Another patient had diarrhea, moderate hematochezia (substantial amounts of intestinal mucosa were observed in the stool specimens), anal stenosis; ulcers involving large areas of the intestinal wall were complicated with polypoid hyperplasia were noted by colonoscopy. Crohn's disease was suspected based on clinical findings in this patient; however, not confirmed by pathologic examination. The hematochezia was alleviated after ileostomy; however, the parents declined empirical drug treatment. High-degree stenosis to atresia in multiple sites of the colon was observed by colonoscopy in the follow-up 6 months later. The patient is now undergoing empirical drug treatment with glucocorticoids combined with metronidazole.

One patient was pathologically-diagnosed with intestinal tuberculosis (the patient had been treated with a transverse colon colostomy in a local hospital), and the patient is still receiving anti-tuberculosis treatment.

### **Discussion**

Perianal infection is common in infants. The clinical manifestations of perianal infection include varying degrees of perianal swelling and abscess formation. Most of the infants with perianal infections can be adequately treated using conservative treatment and abscess incision and drainage; few infants have recurrent perianal abscesses, which may lead to fistula formation. Mild cases of perianal infections have a single fistula, while some severe cases of perianal infections have multiple fistulas, which can be successfully treated by surgery without any complications. Very few infants have from persistent severe anal and rectal infections, and are rarely complicated by

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**Table 2.** Etiological diagnoses of seven younger children with chronic complex anal and rectal inflammation

No.	Gen-der	Colonoscopy findings	Pathologic findings	Diagnosis	Treatment efficacy	Results of follow-up
1	Male	1. Left hemicolon inflammation; 2. Red swelling and erosion of the intestinal wall	Chronic inflammation of the mucous membrane	Clinically diagnosed as Crohn's disease	1. Elimination of the inflammation; 2. Self-cure of fistula	Relapse-free
2	Male	1. Sigmoid colon and rectal inflammation; 2. Red swelling and erosion of the intestinal wall	1. Chronic inflammation of the mucous membrane; 2. Inflammatory granuloma	Pathologically diagnosed as Crohn's disease	1. Elimination of the inflammation; 2. Self-cure of fistula; 3. Disappearance of stenosis	Relapse-free
3	Female	1. Pancolitis, 2. Red swelling and erosion of the intestinal wall; 3. Multiple polypoid hyperplasias; 4. Intestinal stenosis	Chronic inflammation of the mucous membrane	Suspected Crohn's disease	Undergoing empirical drug treatment	Undergoing follow-up
4	Male	1. Left hemicolon inflammation; 2. Multiple polypoid hyperplasia; 3. Intestinal stenosis	1. Chronic inflammation of the mucous membrane; 2. Inflammatory granuloma	Pathologically diagnosed as Crohn's disease	1. Elimination of the inflammation; 2. Self-cure of fistula; 3. Disappearance of stenosis	Relapse-free
5	Male	1. Sigmoid colon and rectal inflammation; 2. Red swelling and erosion of the intestinal wall	Chronic inflammation of the mucous membrane	Suspected Crohn's disease	Undergoing empirical drug treatment	Undergoing follow-up
6	Female	1. Left hemicolon inflammation; 2. Red swelling and erosion of the intestinal wall	Chronic inflammation of the mucous membrane	Clinically diagnosed Crohn's disease	1. Elimination of the inflammation; 2. Self-cure of fistula	Relapse-free
7	Male	1. Left hemicolon inflammation; 2. Multiple polypoid hyperplasia; 3. Intestinal stenosis	1. Chronic inflammation of the mucous membrane; 2. Positive acid-fast staining	Pathologically diagnosed as intestinal tuberculosis	Undergoing anti-tuberculosis treatment	Undergoing follow-up

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anal inflammatory stenosis or multiple fistulas. For such chronic complex anal and rectal inflammation, the primary cause of the disease, usually attributed to improper diet, children delicate skin and unwashed perianal care, can be easily neglected or misdiagnosed. As a result, the palliative treatment scheme often leads to recurrences or exacerbations, or even unnecessary surgery, such as colostomies. In this group of 7 patients, accompanying symptoms were not evident, with the exception of local inflammation. Previous data showed that although perianal infections can be relieved partially with anti-inflammatory treatment, persistence may occur and lead to refractory infections, ultimately resulting in uncommon complications, such as complex fistulas and anal inflammatory stenosis, which cannot be cured by local treatment. The growth and development status of the seven patients were significantly less than normal peers who were treated at our hospital. The perianal manifestations, which were significantly different from common perianal abscesses, included perianal inflammatory scar hyperplasia. Some children had anal stenoses and complex anal fistulas. Although the abnormal laboratory test results were non-specific, taking the possibility of primary disease into account, we further performed colonoscopies to confirm the judgment and formulate a treatment plan.

It is reported that 17%-50% patients with Crohn's disease are complicated with fistulas, 54% of whom have anal fistulas (but ulcerative colitis is never associated with perianal fistulas) [1]; the pathogenesis has not been elucidated. Currently, IBDs are presumed to be caused by excessive congenital or acquired immune responses to intestinal symbiotic microorganisms in genetically-susceptible populations. Most of the affected patients are young and middle-aged; however, the incidence in children is on the rise. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the incidence of Crohn's disease in children increased from 0.1/100,000 thirty years ago to 4.6/100,000 in 2003; the incidence of ulcerative colitis in children increased from 0.5/100,000 to 3.2/100,000 [2]. Currently, inflammatory bowel diseases (IBD) epidemiologic data are unavailable for children in China; however, the clinical observations have indicated that IBD in children tends to occur at a

younger age. Of 7 patients in this group, 4 were confirmed to have Crohn's disease at 13-18 months of age when affected. With respect to the infant with diarrhea and moderate hematochezia, who was suspected to have Crohn's disease and is still undergoing empirical drug therapy, the age of onset was only 6 months after birth. Based on investigations involving IBD, Watson et al. [3] of Liverpool University in UK raised one of the ten questions that have yet to be answered was "what are the factors that determine the timing of the initial attack of inflammatory bowel disease and subsequent relapses?"

The laboratory results in this group of patients showed that there were significant limitations for disease diagnosis by serum antibody detection. For example, it was reported that the diagnostic sensitivity of C-ANCA for IBD is 60%-80% [4], while 2 cases with weakly-positive C-ANCA in this group were eventually diagnosed with Crohn's disease and intestinal tuberculosis. Furthermore, tuberculosis antibody, T-spot, and PPD tests were all negative in the patient with intestinal tuberculosis; this may be due to the immaturity of the immune system in children, who may not be able to produce antibodies against the antigens. But this conflicts with the fact that all seven patients in the study had normal immune functions, but did not produce antibodies. In addition, it is suggested [4] that antibodies with specificity lower than the sensitivity should not be used as screening tools, positive results of antibody detection are insufficient to diagnose IBD, and endoscopy and other inspection methods should be combined to establish a final diagnosis.

In this group, lesions of the four patients confirmed to have Crohn's disease were located in the colon under endoscopy. It has been reported that the incidence of colonic lesions in Crohn's disease was 32% [5]. In our patients, endoscopies did not show characteristic manifestations, with the exception of two patients with multiple polypoid hyperplasia complicated by intestinal stenosis. Such results might be related with the small size of the samples, which also suggests the limitations of the diagnostic value of endoscopy in colonic Crohn's disease. In addition, it is difficult to differentiate hyperplastic or healing intestinal tuberculosis from Crohn's disease using endoscopy because both are manifested by mucosal con-

gestion, edema, erosion, ulceration, inflammatory polyps, and intestinal stenosis [6]. The endoscopic findings of one patient with intestinal tuberculosis in this group were similar to children with Crohn's disease, thus pathologic examinations were required to establish a final diagnosis.

The typical histopathologic findings play important roles in disease diagnosis and developing a differential diagnosis. Observations under the microscope for all four patients with Crohn's disease in this group did not show full-thickness inflammatory changes, which might be closely related with the small size, shallow site, and small range of biopsy tissues. Therefore, multi-site biopsies (including diseased tissues, normal tissues, tissues surrounding the lesions, and each segment affected by lesions) and deep punch biopsies should be recommended to enhance the positive rate of biopsy specimens [7]. In addition, histopathologic examinations of intestinal mucosa biopsy specimens from the seven patients all showed chronic inflammation of mucous membranes; only two patients were diagnosed to have Crohn's disease based on inflammatory granulomas under microscopy. It has been reported that the pathologic diagnosis of Crohn's disease depends on the presence of mucosal lesions accompanied by transmural inflammation or granulomas; the former occurred in 40% of patients with Crohn's disease, and the later occurred in up to 60% of patients [8]. However, it is difficult for the pathologist to differentiate Crohn's disease from intestinal tuberculosis, both of which are manifested as granulomatous inflammation on histologic examination. Ouyang [9] reported that small, scattered granulomas often suggest Crohn's disease, and large, accumulated granulomas often indicate intestinal tuberculosis. However, the detection rates of the specific markers for realistic diagnosis of intestinal tuberculosis are <30% [10-12], and highly specific diagnostic markers for Crohn's disease have not been found. Therefore, when the differential diagnosis of Crohn's disease and intestinal tuberculosis is difficult, both domestic and foreign scholars stress the necessity to undertake empirical anti-TB treatment [13-15].

In summary, the most important limiting factor of this study is the very small number of patients, which make it impossible to draw any

conclusion as what is the uniform approach applicable to clinical practice. But this may enhance clinicians' awareness of the diagnosis of primary cause of the disease and consider the possibility of Crohn's disease or intestinal tuberculosis in younger children. Local surgery is sometimes unnecessary. Empirical drug treatment should be used if necessary as auxiliary diagnosis and treatment to reduce misdiagnosis and inadequate treatment.

### Disclosure of conflict of interest

None.

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