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CASE REPORT

Inflammatory Bowel Disease in Thai Children: Presentations and Outcomes of Treatment

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SUMMARY Inflammatory bowel disease (IBD) is characterized by idiopathic chronic intestinal inflammation, due to abnormalities in gastrointestinal immunoregulation. Pediatric IBD has been rarely reported in Thailand. We describe eight children, five girls and three boys, who were diagnosed with IBD at Ramathibodi Hospital during 1999-2005 and had a follow-up of more than one year. Four cases had Crohn's disease (CD) and four cases had ulcerative colitis (UC). The ages at diagnosis ranged from 3.5 to 15.5 years. Diagnosis of IBD was delayed for more than 12 months in five patients. Five out of eight patients had early onset of disease, before 6 years of age. The manifestations included chronic diarrhea, abdominal pain, rectal bleeding and perianal lesions. The common extraintestinal manifestations were oral ulcer, anemia, weight loss and failure to thrive. Most patients had moderate to severe diseases and ileocolic fistula developed in one patient with CD. The disease was controlled with 5-aminosalicylic acid and corticosteroid in most patients. Four patients required additional therapy with azathioprine. Infliximab was used in two patients who were chronically steroid-dependent CD, one also had persistent ileocolic fistula and both patients responded well. During the follow-up period ranging from 1.1 to 5.8 years, three patients remained growth retardation; all had early onset of disease before 6 years of age, long duration of symptoms of more than 3 years before diagnosis and had multiple relapses. It is concluded that there is an increasing number of IBD in Thai children during the recent years. Most patients had moderate to severe diseases. Early onset of disease, delay in diagnosis and treatment are responsible for more complications, particularly persistent growth impairment. Early recognition of IBD and treatment are essential for a satisfactory long-term outcome.

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation of unknown etiology. The pathogenesis of IBD is likely to be associated with an inappropriate immune response triggered by genetic and environmental factors.[1,2] It presents in two major forms: ulcerative colitis (UC) and Crohn's disease (CD). Anatomically, the inflammation in UC is usually limited to the rectum and colon whereas CD can involve the whole of the gastrointestinal (GI) tract. For the extents of inflammation, UC is confined to the mucosa while CD has transmural involvement.[1] In at least 25% of patients, IBD manifests itself during childhood or adolescence.[3] The incidence of IBD is lower in children than in adults, however, the

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childhood disease has a relatively more complicated course due to associated growth and developmental problems. The incidence of IBD is much higher in the Western countries than in Asia. To date, apart from the Middle-East region, there have been only few reports of pediatric IBD in other Asian countries.[4-7] In Thailand, there has been only one reported case of IBD in children.[8] We therefore describe children with the diagnosis of IBD in our center.

PATIENTS AND METHODS

During a 7-year period (January 1999-December 2005)**,** children who were diagnosed with IBD at Ramathibodi Hospital and had a follow-up of more than 1 year were included in the study. At the time of diagnosis, all patients had upper endoscopy and colonoscopy with histological examination of intestinal biopsies, and small bowel follow-through. The severity of disease in CD was assessed by pediatric CD activity index (PCDAI) score: ≤ 10 as inactive, 11-30 as mild and ≥ 31 as moderate to severe.[9] For UC, the disease activity was determined as mild, severe and fulminant following the classification by Truelove and Witts,[10] using five criteria of temperature, pulse rate, hemoglobin, erythrocyte sedimentation rate, and bowel frequency. Investigations for the exclusion of infective enterocolitis were performed in all cases. Cow's milk protein allergy was excluded in those who had presenting symptoms during the first three years of age.

RESULTS

Ten children, aged 3.5-15.5 years, were diagnosed with IBD, six with CD and four with UC. Two patients with CD were excluded from the study. One had poor compliance and was lost to follow-up. Another one had a follow-up period less than one year. Seven of the eight patients were Thai but one was Indian (case 6).

Clinical manifestations

The ages at diagnosis ranged from 3.5 to 15.5 years. Five out of eight patients had early onset of disease, before 6 years of age. Five of the eight patients had duration of symptoms more than 1 year

Table 1 Demographic data, clinical manifestations, extent of gastrointestinal (GI) involvement and the disease severity

Case	Dx	Sex	Age (years)		Manifestations		Extent of GI involvement*	Severity**
			Onset	Dx	GI	Extraintestinal		
1	CD	F	5	10	Bloody diarrhea, abdominal pain	Oral ulcers, arthralgia, FTT, anemia	C, TI, I, J, S	PCDAI score 67.5
2	CD	F	0.6	15.5	Diarrhea, perianal skin tags	Pubertal delay, FTT, anemia	C, TI, I, J, D, S, ileocolic fistula	PCDAI score 52.5
3	CD	M	9.9	12.9	Diarrhea	Weight loss, anemia	C, TI, I	PCDAI score 42.5
4	CD	M	11.9	12.1	Abdominal pain	Prolonged fever, oral ulcers, weight loss	TI, S	PCDAI score 57.5
5	UC	F	5.5	6	Bloody diarrhea, perianal skin tags	Weight loss, anemia	R, C	Severe
6	UC	F	4.4	7.5	Bloody diarrhea	DVT left leg, dural sinus thrombosis, anemia	R, C	Severe
7	UC	F	2	3.5	Bloody diarrhea, hepatomegaly	AIH	R, C	Mild
8	UC	M	14.2	14.5	Rectal bleeding	-	R, C (left side)	Mild

*Assessed by upper endoscopy, colonoscopy and small bowel follow-through;
**Assessed by Pediatric Crohn's disease activity index (PCDAI) score[9] for Crohn's disease and Truelove and Witts's classification for ulcerative colitis.[10]
Dx, diagnosis; CD, Crohn's disease; UC, ulcerative colitis; FTT, failure to thrive; DVT, deep vein thrombosis; AIH, autoimmune hepatitis; R, rectum; C, colon; TI, terminal ileum; I, ileum; J, jejunum D, duodenum; S, stomach.

prior to the diagnosis of IBD. The most common manifestation was chronic diarrhea, which was bloody in four and watery in two cases. The other manifestations included chronic abdominal pain, rectal bleeding, perianal disease, anemia, weight loss, failure to thrive and extraintestinal manifestations (Table 1). One patient (case 1) had a previous laparotomy due to presentation with symptoms of acute abdomen.

Laboratory findings

The abnormal laboratory findings included anemia in six, thrombocytosis in six, elevated ESR in five, and hypoalbuminemia in six cases (Table 2). Case 7 had abnormal liver function tests as follow: serum alanine aminotransferase, 355 U/l; aspartate aminotransferase, 318 U/l; alkaline phosphatase, 606 U/l; gamma glutamyl transpeptidase, 268 U/l; total bilirubin, 0.4 mg/dl; and direct bilirubin, 0.2 mg/dl. The anti-nuclear antibody of this case was positive titer > 1:256.

Extent of intestinal involvement

In patients with CD, colonoscopy revealed colitis and ileitis with or without ulcers in three cases (Table 1). One patient had ileal ulcers without colonic involvement. Upper endoscopy revealed small gastric ulcers in three cases and duodenal ulcers in one case. Small bowel lesions, swelling or loss of mucosal fold or narrowing (Fig. 1) were demonstrated by small bowel follow-through in all cases with CD and ileocolic fistula was detected in one patient. Three of the four cases of UC had proctitis and pancolitis demonstrated by colonoscopy. One patient had left-sided colitis.

Histopathology

The histopathology of colonic biopsies of all patients revealed acute inflammation with cryptitis

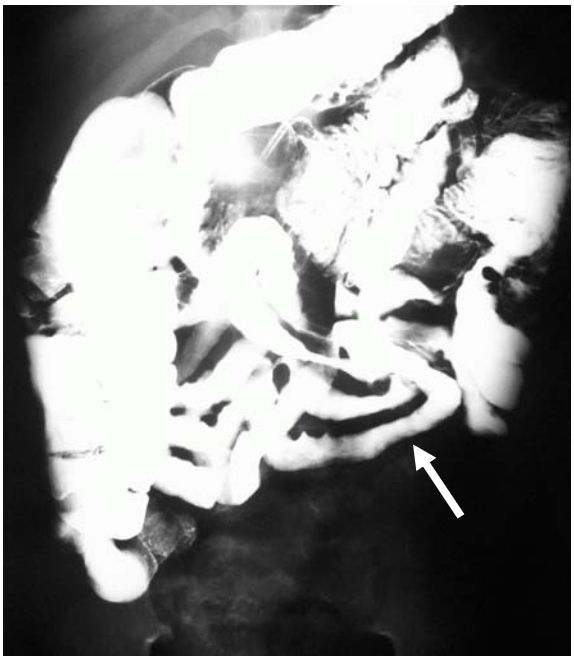

Fig. 1 Small bowel follow-through in a patient with Crohn's disease (case 3) demonstrated a loss of ileal mucosal folds with narrowing of its lumen from fibrosis secondary to chronic transmural involvement (arrow).

Table 2 Laboratory data of the patients at the time of diagnosis

Case	Hct (%)	WBC ($\times 10^3$/μl)	Platelet ($\times 10^3$/μl)	ESR (mm/hour)	Albumin (g/l)
1	21	12.0	1,086	37	30
2	24	9.5	1,002	47	26
3	28	9.4	1,052	20	26
4	30	14.0	618	81	29
5	27	22.6	643	49	22
6	26	23.2	712	33	26
7	35	12.4	410	10	41
8	41	8.9	402	10	44

Hct, hematocrit; WBC, white blood cells; ESR, erythrocyte sedimentation rate.

and chronic inflammation with crypt distortion, which were compatible with IBD. Acute and chronic ileitis was demonstrated in all cases with CD. Non-caseating granulomas were noted in the colonic tissue samples of one patient (case 3) with negative acid fast stain (Fig. 2). Erosive gastritis was found in cases 1 and 2. Duodenitis with ulceration was found in case 2. Liver histology in case 7 showed portal inflammation and piecemeal necrosis compatible with chronic active hepatitis.

Treatment and outcomes

Seven patients (cases 1-7) were initially treated with prednisolone for at least 4 weeks and then prednisolone was gradually tapered off (Table 3). Case 8 was initially treated with mesalazine (5-aminosalicylic acid, 5-ASA). Maintenance therapy composed of mesalazine in all patients and combined with azathioprine in four patients, two cases with CD and two cases with UC. Metronidazole was added in case 2 for fistula and perianal disease. Corticosteroid was intermittently given for controlling of relapsed active diseases. Three patients (cases 1, 2 and 6) became chronic steroid-dependent. Although colitis in case 7 was not severe, a low dose of corticosteroid was used for maintenance therapy for controlling autoimmune hepatitis. Infliximab, anti-TNF-α, was initiated in two patients due to chronic steroid-dependent CD (cases 1 and 2) and persistent ileocolic fistula (case 2). Case 1 received infliximab (5 mg/kg body weight) at 8-week intervals and was able to reduce prednisolone dosage from daily 15 mg to 2.5 mg. The ileocolic fistula in case 2 dramatically closed after receiving three doses of infliximab (5 mg/kg body weight) at 0, 2 and 6 weeks, respectively.

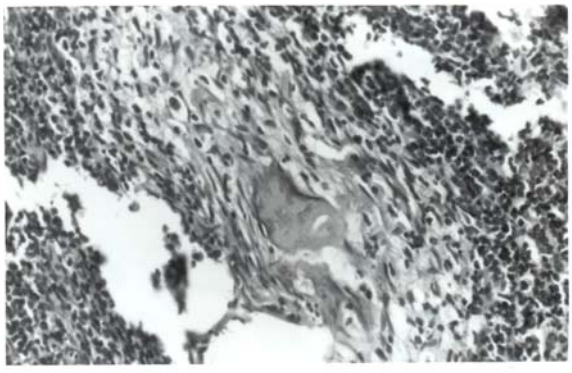

Fig. 2 Colonic biopsy in a patient with Crohn's disease demonstrated a noncaseating epithelioid granuloma (hematoxylin and eosin; ×200).

During the follow-up period ranging from 1.1 to 5.8 years, six patients had chronic courses with intermittent relapses and remissions. Cases 4 and 8 remained in remission and had no disease relapse. At the time of this report, all patients remained well on maintenance therapy. None required surgical management. At the most recent follow-up, three patients (cases 1, 2 and 6) were found to have persistent short stature (Z-score for height < -2) while the rest had normal growth (Table 3).

DISCUSSION

IBD is an uncommon disease in Asian countries. In Thailand, there have been few reports of UC and CD in adults[11,12] and only one reported case of UC in children.[8] In our hospital, which is a referral medical center in Bangkok, pediatric IBD had not been diagnosed until 1999 when pediatric colonoscopy became routine. During the 7-year period, ten children were diagnosed as having IBD; six with CD and four with UC. Two patients with CD were excluded from the study because the duration of follow-up was less than one year. Although IBD is uncommon in Thai children, the number of patients is increasing in recent years. This could be due to an improved diagnostic modality or could represent the actual rise of the prevalence of IBD among Thai children. Recent reports from Western countries and Taiwan suggest that the prevalence of childhood CD is rising.[3,4] Whether the prevalence of IBD is truly increasing among Asian children is not clear. Due to the rarity of IBD in this region, a multi-center study is required to verify the true prevalence.

The clinical presentations in this case series are comparable to those reported in the literatures.[1,3-6] However, early age of onset before 6 years was common in this report, occurring in five of the eight patients. Data from a large pediatric IBD registry of 1,370 children, 15% was diagnosed before 6 years of age and 1% was diagnosed in infants.[13] Extraintestinal manifestations including liver, eye, joint, skin, oral and vascular diseases were common and occurred in 25-35% of patients with IBD.[1,3] However, autoimmune hepatitis and thromboembolic disease,

Table 3 Treatment of IBD and outcomes

Case	Treatment	FU (years)	Clinical course	Z-score			
				Weight		Height	
				Before Rx	Last visit	Before Rx	Last visit
1	PD, 5-ASA, AZA, infliximab	3.5	Multiple relapses, steroid-dependent until infliximab Rx	-2.6	-2.3	-2.3	-3.2
2	PD, MT, 5-ASA, AZA, infliximab	3.0	Steroid-dependent, persistent ileocolic fistula until Infliximab Rx	-5.5	-3.5	-6.1	-5.3
3	PD, 5-ASA	2.3	One relapse then remission	-2.2	0.0	-0.9	-0.1
4	PD, 5-ASA	1.2	No relapse	-1.0	0.5	0.9	1.7
5	PD, 5-ASA, AZA	5.8	Few relapses then remission	0.0	0.7	0.2	0.5
6	PD, 5-ASA, AZA	5.5	Multiple relapses	-2.5	-0.7	-2.2	-3.2
7	PD, 5-ASA	2.9	One relapse then remission	-0.3	0.5	-0.2	0.0
8	5-ASA	1.1	No relapse	1.1	1.0	1.0	0.7

FU, duration of follow-up; Rx, treatment; PD, prednisolone; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MT, metronidazole

found in our patients, were rarely reported in IBD patients.[3,14,15] All patients with CD in this study had moderate to severe diseases as indicated by PCDAI score.[9] Two of the four cases of UC had severe diseases according to Truelove and Witt's classification.[10] The contributing factor for the severity is most likely due to the delay in diagnosis as well as treatment. Most of our patients had a long duration of symptoms, typically more than 1 year, prior to referral to our institution. The delay in diagnosis and referral was mainly due to the rarity of IBD in Thai children and under recognition by primary care physicians. Pediatricians should be aware of IBD in children with chronic diarrhea or chronic abdominal pain. The associated findings suggestive of IBD include anemia, failure to thrive, perianal diseases, extraintestinal symptoms, elevated ESR and thrombocytosis.

The diagnosis of IBD requires colonoscopy and histological examination. If CD is suspected, upper endoscopy and small bowel follow-through are performed for evaluating upper GI and small intestinal involvement. The histopathologic findings in UC compose of acute inflammation of colonic mucosa with neutrophilic infiltrate in mucosa with cryptitis and crypt abscesses, together with signs of chronicity including lymphoid aggregates, plasma cells, mast cells and eosinophils in lamina propria and distortion of crypt architecture.[1] For CD, the pathologic hallmark is segmental inflammation and transmural inflammation to all layers of bowel wall.[1] The histopathology of mucosa may resemble UC. Granuloma is the characteristic finding of CD but it is not always found. They are found more commonly in submucosa than mucosa. They are observed in 60 percent of surgical specimens but less frequently, in 20 to 40 percent of mucosal biopsies.[16] In this study, granulomas were found in mucosal biopsies in one case of CD.

The pathogenesis of IBD remains unclear. The recent hypothesis is that IBD results from an inappropriate mucosal immune response to the mucosal microflora or enteric bacteria. Inflammation can occur as a result of either excessive effector T-cell function or deficient regulatory T-cell functions.[2] Once the mucosal immune system is activated, cytokines and chemokines play important roles in the promotion and amplification of the inflammatory cascades. Recent studies indicate that TNF-α is a key pro-inflammatory cytokine processing many properties relevant to intestinal inflammation in CD.[17]

The goal of treatment for IBD is to induce and maintain clinical remission and improve nutritional status. The conventional drug regimen includes corticosteroid, 5-ASA and azathioprine. 5-ASA is effective as monotherapy to induce remission

in mild colitis and prolong remission in UC. Corticosteroid is effective for controlling the active inflammation both in UC and CD of moderate and severe disease.[1] Azathioprine is an immunomodulatory agent using for controlling intestinal inflammation and maintaining the remission in moderate and severe CD and UC.[18] Addition of azathioprine allows reduction and eventually discontinuation of corticosteroid. Seven of the eight patients in this report required corticosteroid therapy for controlling active diseases. Additional therapy with azathioprine was used in 2 patients with CD and 2 patients with severe UC due to disease relapsed after reduction of corticosteroid. Recently, infliximab, a chimeric (murine-human) monoclonal antibody directed against TNF-α, has been available in our country. Infliximab has been shown to be effective for treatment of refractory CD and fistula disease.[19,20] After initial two or three doses of infliximab, maintenance therapy at 8-week interval for one year results in prolonged remission.[21] Infliximab was used in two patients who were chronically steroid-dependent CD and one of them had persistent ileocolic fistula despite conventional treatment for 21 months. Maintenance therapy with infliximab was not given in case 2 due to its high cost and the patient's financial problem. Short-term follow-up after infliximab therapy showed satisfactory clinical outcomes. However, a longer duration of follow-up is required for both patients.

Growth impairment is an important issue in pediatric patients with IBD.[1,3] Long-term follow-up in this study showed that three patients (cases 1, 2 and 6) continued to have severe growth retardation with very low height Z-score, despite of appropriate medical treatment and nutritional support. All of them had an early onset of disease (before 6 years of age) and a long-standing active disease of more than 3 years before treatment. It is widely accepted that IBD has significant effects on nutritional status, mainly due to a combination of decreased intake and increased metabolic demands.[3] Long-standing uncontrolled diseases have more impact on nutritional status, especially for CD which malabsorption of nutrients can occur due to small intestinal inflammation. At the time of diagnosis, all patients had very poor nutritional status with Z-score for weight and height below -2. Moreover, these patients had multiple relapses requiring long durations of corticosteroid therapy. Long-term use of corticosteroid can cause adverse effects particularly suppression of linear growth.[22] Early recognition of IBD and early treatment are essential for reducing the severity and frequency of complications, particularly growth retardation. To achieve optimal linear growth, apart from comprehensive nutritional support, an attempt to control intestinal inflammation with other alternative medications instead of chronic corticosteroid use should be considered.

It is concluded that there is an increasing number of IBD in Thai children during the recent years. Most patients had moderate to severe diseases. Early onset of disease, delay in diagnosis and treatment are responsible for more complications particularly persistent growth impairment. Early recognition of IBD and treatment are essential for a satisfactory long-term outcome.

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