Variable outcome in infantile-onset inflammatory bowel disease in an Asian cohort

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AIM

Infantile-onset inflammatory bowel disease (IO-IBD) with the onset of disease before 12 mo of age, is a different disease entity from childhood IBD. We aimed to describe the clinical features, outcome and role of mutation in interleukin-10 (IL-10) and interleukin-10 receptors (IL-10R) in Asian children with IO-IBD.

METHODS

All cases of IO-IBD, defined as onset of disease before 12 mo of age, seen at University Malaya Medical Center, Malaysia were reviewed. We performed mutational analysis for IL10 and IL10R genes in patients with presenting clinical features of Crohn’s disease (CD).

RESULTS

Six [13%; CD = 3, ulcerative colitis (UC) = 2, IBD-unclassified (IBD-U) = 1] of the 48 children (CD = 25; UC = 23) with IBD have IO-IBD. At final review [median (range) duration of follow-up: 6.5 (3.0-20) years], three patients were in remission without immunosuppression [one each for post-colostomy (IBD-U), after standard immunosuppression (CD), and after total colectomy.
(UC)]. Three patients were on immunosuppression: one (UC) was in remission while two (both CD) had persistent disease. As compared with later-onset disease, IO-IBD were more likely to present with bloody diarrhea (100% vs 55%, P = 0.039) but were similar in terms of an associated autoimmune liver disease (0% vs 19%, P = 0.31), requiring biologics therapy (50% vs 36%, P = 0.40), surgery (50% vs 29%, P = 0.27), or achieving remission (50% vs 64%, P = 0.40). No mutations in either IL10 or IL10R in the three patients with CD and the only patient with IBD-U were identified.

CONCLUSION
The clinical features of IO-IBD in this Asian cohort of children who were negative for IL-10 or IL-10R mutations were variable. As compared to childhood IBD with onset of disease after 12 mo of age, IO-IBD achieved remission at a similar rate.

Key words: Infantile-onset inflammatory bowel disease; Pediatric

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Core tip: We described the clinical features, outcome and role of mutation in IL-10 and IL-10R in Asian children with infantile-onset inflammatory bowel disease (IO-IBD). We reviewed all cases of IO-IBD, defined as onset of disease before 12 mo of age, seen at a single center in Malaysia. We conclude that the clinical features of IO-IBD in this Asian cohort of children were variable. IO-IBD achieved remission at a similar rate, were more likely to discontinue immunosuppression therapy at final review and not more likely to require biologics therapy or surgery.

INTRODUCTION
Most of the patients with inflammatory bowel disease (IBD) have the onset of disease during adolescence or early adulthood[1-2]. There is a well-documented increase in the incidence of IBD with an onset of disease within the first two decades of life[3]. In childhood IBD, the disease phenotype and subsequent disease course are influenced by the age at first diagnosis[4]. In a large North American cohort of childhood IBD, those who had an onset of disease between 1 to 5 years (very early-onset) were more likely to have a mild disease at diagnosis but a more aggressive phenotype over time as compared to children who had an onset between 6 to 10 years of age[5].

The development of IBD in infancy is extremely rare[11]. Data from epidemiological studies and IBD registries, mostly from North America and Europe, suggest that less than 1% of children with IBD have an onset during the first 12 mo of life[5-9]. Crohn’s disease (CD) appeared to be more common than ulcerative colitis (UC) in these studies[5-8]. However, a recent large cohort study from North America involving close to 2000 cases of childhood IBD did not identify any cases with an onset of disease < 1 year of age[4].

The current concept of the pathogenesis of IBD is that it develops in genetically susceptible hosts with an altered intestinal response to various external stimuli[10,11]. In infantile-onset (IO-) IBD, monogenic diseases causing persistent intestinal inflammation, such as Wiskott-Aldrich syndrome and hyper-IgM syndrome, are well documented[12,13]. Mutations in genes encoding the interleukin-10 (IL10) or interleukin-10 receptors (IL10R) subunit proteins have been discovered in patients with IO enteroocolitis, usually within the first three months of life[14-18]. These infants have severe perianal disease and extra-intestinal features such as folliculitis and arthritis[14-17]. In some cases, hematopoietic stem cell transplant (HSCT) is curative in IBD secondary to IL10/IL10R deficiency[14-17]. Nevertheless, it has been shown that the majority of patients with severe infantile colitis produce and respond to IL10 normally[15], suggesting additional pathways to inflammation and the complex nature of the pathogenesis of infantile-onset inflammatory bowel disease (IO-IBD)[19].

IBD is not as common in Asians as in the Caucasians[20]. We reported the first case of IO-IBD in an Asian infant due to mutations in the IL10R by using exome sequencing[21]. Subsequently, other authors have also reported early-onset IBD due to mutations in IL-10R[22]. The aims of the present study were to describe the phenotypic characteristics and outcome of IO-colitis in a cohort of Asian children and to define the role of IL10 and IL10R mutations in these patients.

MATERIALS AND METHODS
The present study was a retrospective review of all patients with childhood IBD who were seen at the Department of Paediatrics, University Malaya Medical Center (UMMC), Kuala Lumpur, Malaysia, from 1996 to 2014. During the study period, UMMC was the major referral center for pediatric IBD for entire Malaysia, serving both peninsular Malaysia and East Malaysia. The present study was funded by the High Impact Research Fund from Ministry of Higher Education, Malaysia (UM.C/625/HIR/MOHE/CHAN/13/1) and was approved by the institutional ethical committee of UMMC (UMMC 975.7). Written informed consent was given by the parents of the children for their clinical record, as well as the results of the mutational analysis to be used in the present study.

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Patients
The medical records of all children younger than 18 years of age who have a diagnosis of IBD were reviewed. Patients who have the onset of the disease in the first 12 mo of age were included. Data on all children aged ≤ 18 years of age with a diagnosis of IBD who are currently followed up at the department were also reviewed. The following patients were excluded: (1) patients with incomplete medical data; or follow-up or outcome data were incomplete; and (2) patients with an alternative diagnosis, such as infective, allergic, or iatrogenic (i.e., radiation colitis or graft-vs-host diseases) causes of colitis.

Diagnosis
The patients were diagnosed to have CD, UC or IBD Unclassified (IBD-U) according to established clinical, biochemical, radiologic, endoscopic, and histologic criteria. In UMMC, all patients suspected of having an IBD were investigated according to the recommendations by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. In addition, congenital or acquired immune deficiencies causing infantile colitis such as human immunodeficiency virus infection (HIV), severe combined immune deficiency (SCID), chronic granulomatous disease, hyper-IgM syndrome, and Wiskott-Aldrich syndrome were excluded by complete blood count, platelet count, peripheral blood film, HIV serology, immunoglobulins level (IgG, IgA, IgM and IgE), lymphocyte subset, nitroblue tetrazolium test, and anti-enterocyte antibody.

The diagnosis of IBD required endoscopic evaluation, including histologic assessment of mucosal pinch biopsies. All patients underwent esophagogastroduodenoscopy (EGDS) and colonoscopy. Multiple mucosal biopsies were reviewed by clinical pathologists. Stool studies were performed in all patients to exclude infectious causes of diarrheal illness. Disease location and behavior were classified according to the Paris Classification of Pediatric IBD. Features which favor the diagnosis of CD are extensive endoscopic inflammation of the upper gastrointestinal tract; presence of perianal disease; normal looking rectum; presence of stenosis, cobblestoning, and linear ulceration in the ileum; and macroscopic ileitis in the presence of normally looking cecum. Histological features favoring CD include microscopically normal appearing skip lesions as well as presence of well-formed granuloma remote from ruptured crypts.

Medical therapy
In children with CD, exclusive enteral nutrition (EEN) was the initial treatment of choice. In children who were unable to comply with EEN, or who did not respond to EEN, corticosteroid (CS; 1-2 mg/kg body weight, maximum 60 mg) was the initial immunosuppression of choice. Azathioprine (Aza) at a maximum dose of 2.5 mg/kg body weight was used as steroid-sparing drug. Monitoring of the therapeutic levels for Aza or determination of thiopurines methyltransferase genotype or phenotype were unavailable in the unit throughout the study period. The clinical response to Aza was closely observed while its side effects such as acute pancreatitis and marrow suppression were regularly monitored. Infliximab (IFX) was used in children with refractory disease, fistulating CD, or in luminal CD despite optimal immunomodulatory therapy. IFX was administered in dose of 5 mg/kg body weight at weeks zero, two and six, followed by 8-weekly infusions. This dosing regimen was adjusted according to the response of the patients, either by shortening the duration between two consecutive infusions, or an increase in the dose administered (maximum 10 mg/kg). No therapeutic level of IFX or antibodies against IFX was available within the country or the region during the study period. Adalimumab (Ada) was given to patients who developed a loss of effect to IFX. Ada was administered subcutaneously at week zero and two (160 mg and 80 mg, or 80 mg and 40 mg, for body weight ≥ 40 kg or < 40 kg) and subsequently 40 mg every other week irrespective of body weight.

Data collection
The following data were collected: demographic data, clinical features, radiologic and histologic findings, medical and surgical therapies if applicable, and disease status at final review. Patients with CD were considered to have inactive disease if the Pediatric Crohn Disease Activity Index score was ≤ 10, while patients with UC were considered to be in remission if the Pediatric Ulcerative Colitis Index score was ≤ 10.

Comparisons were made between patients with IO-IBD and patients who have an onset of disease after the first year of life (defined as later-onset disease) in their presenting features, immunosuppressive therapy and the need for surgery, as well as disease status at final review.

Mutational analysis
Blood samples were obtained from patients and their parents for mutational analysis after obtaining written informed consent. The analysis was performed at the Research Laboratory of the Department of Paediatrics and Adolescent Medicine, the University of Hong Kong. The genomic PCR was performed using the HotStar-Taq® Plus PCR system (Qiagen GmbH, Germany). Between 10-100 ng of genomic DNA was amplified using the sense and antisense primers, flanking the coding regions and splice junctions, according to the manufacturer’s protocol. DNA sequencing was performed on both strands using BigDye Terminator v3.1 Cycle Sequencing Kit and 3730xl DNA Analyzer (Applied Biosystems CA., United States). Homology analysis with the reference genomic sequence was...
performed using the NCBI program BLAST (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The mutations screened for the purpose of the present study are shown in Supplementary material.

**Statistical analysis**

Data were managed with IBM SPSS statistical package version 21.0.0 for Windows. Dichotomous measures were compared by means Fisher exact test. Statistical significance was set at a $P$ value of $< 0.05$.

**RESULTS**

During the study period, a total of 48 children with a diagnosis of IBD (CD = 25, UC = 23) were followed up at the Department of Paediatrics of UMMC. Of these, six (13%) had the onset of disease within the first year of life (IO-IBD). According to the Paris Classification for Pediatric IBD[24], two of the six patients had UC, three had CD, and one had IBD-U.

**Demography**

There were four males and two females. None of the patients has any first degree family members who also have IBD or other autoimmune conditions. With the exception of patient No. 1, none of the patient had any significant perinatal history. The age of onset of first symptom ranged from first week to 12 mo of life (median 5 mo; Table 1).

**Phenotypic characteristics**

Phenotypically, the patients can be classified into CD ($n = 3$), UC ($n = 2$), and IBD-U ($n = 1$) at initial presentation, but the subsequent disease course was diverse.

**Clinical presentation**

All the children presented initially with bloody diarrhea (Table 1). One patient was diagnosed to have postnatal cytomegalovirus (CMV) infection at birth. Oral ulcers were noted in one patient with CD while perianal disease was present in two of the three patients with CD and the infant with IBD-U.

**Associated medical and autoimmune conditions**

None of the patients developed other autoimmune diseases. One patient (infant No. 3) developed developmental regression at seven years of age with course tremors. No etiology can be ascertained despite extensive investigations. Investigations for immune system did not reveal the presence of immunodeficiency.

**UC**

Patient No. 1 developed watery, non-bloody diarrhea on third day of life (Table 1), and was started on extensively hydrolyzed and amino acid-based formulae. The diarrhea became bloody from three months onwards. When referred at our center at four months of age, there was no oral ulcer or perianal disease. During bowel rest and total parenteral nutrition, there was no diarrhea, but diarrhea promptly resumed when extensively hydrolyzed formula was introduced. A colonoscopy showed pancolitis with inflamed mucosa and friability but no ulceration. The rectum, sigmoid and descending colon were the most severely affected. Histologically, there was dense lymphoplasmacytic and eosinophilic infiltration of the colonic mucosa. A course of oral CS failed to improve his symptoms. The diarrhea gradually improved with amino acid-based formula. The stool frequency improved but was persistently blood stained.

There was a relapse of bloody diarrhea at sixteen month of age when the child was gradually weaned off from amino acid formula to a normal diet. Repeated courses of CS and a course of oral cyclosporin failed to improve his symptoms. A total colectomy was performed. Macroscopically, the entire colon was pale in appearance with prominent submucosal vascular pattern, indicating mucosal atrophy. No ulcers were noted. Histologically the mucosa was thin. There were areas of patchy inflammation, with evidence of chronic inflammation, dense lymphoplasmacytic infiltration in the mucosa, sparing the submucosa, muscular layer and serosa. There was no crypt branching, or irregularity in the shape and sizes of the crypt. There was also scant eosinophilic infiltration. The child remained symptom free after total colectomy.

**CD**

Patient No. 3 developed symptoms of recurrent bloody diarrhea at the age of seven months (Table 1). A diagnosis of postnatal CMV infection was made at another hospital at the age of three months due to persistent neonatal cholestasis. The IgM for CMV was positive. The jaundice subsided at the age of six months. The bloody diarrhea was intermittent in nature. At referral to our unit at two years of age, the child had failure to thrive, abdominal pain and bloody diarrhea, with multiple perianal fistulae and abscesses. EGDS showed duodenitis. Colonoscopy showed extensive ulceration with pseudopolyps formation. EEN was commenced, together with antibiotics, CS and Aza. IFX was given in view of severe perianal disease. After one year, there was improvement in general condition but minimal improvement in the perianal disease. He was noted to have three episodes of pneumonia and two episodes of herpes zoster infection when he was receiving IFX therapy. However, no recurrent infections were noted when the therapy was discontinued. In addition, investigations into an underlying immunodeficiency were negative.

A defunctioning colostomy was performed at six years of age. There was persistent perianal disease. A course of Ada (six doses) was given with no improvement. A repeat colonoscopy showed extensive

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colonic ulceration. There was persistent and severe perianal disease. EEN (amino acid-based formula) was recommenced in addition to low dose CS (10 mg). Repeated courses of oral antibiotics (amoxicillin, doxycycline, metronidazole and vancomycin) were also given\cite{30}. The condition improved with this regime with a reduction of the number of bloody stools. The perianal disease became quiescent with no abscess or fistula.

**IBD-U**

Infant #6 developed chronic bloody diarrhea at four months of age. She has been breast-fed exclusively since birth. She was given repeated courses of antibiotics even though the stool studies were negative for any pathogens. Subsequently she had several

<table>
<thead>
<tr>
<th>Patients' initials</th>
<th>No. 1</th>
<th>No. 2</th>
<th>No. 3</th>
<th>No. 4</th>
<th>No. 5</th>
<th>No. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Chinese</td>
<td>Chinese</td>
<td>Malay</td>
<td>Chinese</td>
<td>Indian</td>
<td>Malay</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Breast feeding (duration)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (3 mo)</td>
<td>Yes (2 mo)</td>
<td>Yes (4 mo)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>First week</td>
<td>12 mo</td>
<td>7 mo</td>
<td>2 mo</td>
<td>6 mo</td>
<td>4 mo</td>
</tr>
<tr>
<td>Disease phenotype</td>
<td>EC→UC</td>
<td>UC</td>
<td>Oral ulcers, bloody diarrhea, abdominal pain</td>
<td>CD</td>
<td>CD</td>
<td>IBD-U</td>
</tr>
<tr>
<td>Major symptoms at presentation</td>
<td>Bloody diarrhea and PR bleeding</td>
<td>Bloody diarrhea, anaemia</td>
<td>Bloody diarrhea, abdominal pain</td>
<td>Bloody diarrhea, abdominal pain</td>
<td>Bloody diarrhea, growth failure</td>
<td>Bloody diarrhea</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>Nil</td>
<td>Nil</td>
<td>Abscess and fistula</td>
<td>Nil</td>
<td>Abscess and fistula</td>
<td>Abscess and fistula</td>
</tr>
<tr>
<td>Other medical or autoimmune conditions</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Recurrent infections</td>
<td>Nil</td>
<td>Nil</td>
<td>Congenital CMV infection,</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Disease location</td>
<td>E4SI</td>
<td>E4</td>
<td>L3L4a</td>
<td>L3L4a</td>
<td>L3</td>
<td>L2</td>
</tr>
<tr>
<td>Disease behavior/ severity</td>
<td>Colonic mucosa showed mild degenerative atypia, cryptitis and crypt abscesses. Lamina propria showed increase in neutrophilic and lymphoplasmocytic infiltration.</td>
<td>Lyphocytic infiltration of lamina propria. No granuloma or crypt abscess seen. The duodenum showed chronic inflammation.</td>
<td>Lymphocytic infiltration of lamina propria. No granuloma or crypt abscess seen</td>
<td>Mild inflammation in the lamina propria with lymphocytes and plasma cells. No granuloma or crypt abscess</td>
<td>First biopsy: transmural inflammation involving all layers of bowel wall, including the skeletal muscle with dense lymphoplasmocytic infiltration. No crypt abscess seen. Second biopsy: colonic mucosa inflamed but the architecture was preserved. Significant lymphoplasmocytic and neutrophilic infiltration mainly confined to the lamina propria</td>
<td></td>
</tr>
<tr>
<td>Histopathology</td>
<td>L2p</td>
<td>L1B</td>
<td>L3</td>
<td>L2</td>
<td>L1p</td>
<td></td>
</tr>
<tr>
<td>Other associated diseases</td>
<td>Nil</td>
<td>Nil</td>
<td>Developmental regression at 6 yr age</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Mutation analysis</td>
<td>Not done CS, CsA, enteral nutrition</td>
<td>Not done CS, Aza</td>
<td>Not detected EN, CS, Aza, IFX × 24 doses</td>
<td>Not detected Aza, Aza, IFX × 14 doses</td>
<td>Not detected Aza, IFX × 3 doses</td>
<td>Not detected Nil</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>Total colectomy at 18 mo</td>
<td>Ileostomy at 6 yr of age</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Ileostomy; closure at 18 mo of age</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 yr</td>
<td>9 yr</td>
<td>13 yr</td>
<td>18 yr</td>
<td>2 yr</td>
<td>no therapy</td>
</tr>
<tr>
<td>Age at last follow up</td>
<td>21 yr</td>
<td>Alive, in remission; off therapy for 18 yr</td>
<td>Alive, in remission; on Aza</td>
<td>Alive, persistent disease, on CS, Aza. Developmentally delayed.</td>
<td>Alive, in remission; off therapy for 2 yr</td>
<td>Alive, in remission; no therapy</td>
</tr>
<tr>
<td>Final clinical status</td>
<td>Alive, deafness due to aminoglycosides. in remission, off therapy for 18 yr</td>
<td>Alive, in remission; on Aza</td>
<td>Alive, persistent disease, on CS, Aza, and IFX. Parents refused surgery</td>
<td>Alive, in remission; off therapy for 2 yr</td>
<td>Alive, in remission; no therapy</td>
<td></td>
</tr>
</tbody>
</table>

1According to Levine et al\cite{24}. Aza: Azathioprine; CD: Crohn’s disease; CMV: Cytomegalovirus; CS: Corticosteroid; CsA: Cyclosporin; EC: Eosinophilic colitis; EN: Enteral nutrition; IFX: Infliximab; PR: Per rectal; UC: Ulcerative colitis.
perianal abscesses and fistulas requiring incision and drainage. She was seen at another hospital at five months of age, where a limited sigmoidoscopy showed extensive, deep linear ulceration up to the sigmoid colon. A sigmoidal colostomy was performed. Histological examination of the bowel tissue obtained during the operation showed transmural inflammation involving the muscular layer and the serosa. After the colostomy, the child improved with weight gain and a complete cessation of diarrhea. No immunosuppression treatment was started.

When seen at our hospital at seven months of age, the perianal area was quiescent with a skin tag. No abscess was noted. An EGDS was normal. A colonoscopy showed multiple flat nodules with relatively normal mucosa over the rectum. The remaining colon was pale with loss of normal vascular pattern. There were no pseudopolyps, mucosal ulcerations or friability. Histologically, the colonic mucosa was inflamed. The tubular glands were devoid of significant architectural distortion. The lamina propria showed marked infiltration by lymphoplasmacytic cells with the formation of lymphoid follicles and mild neutrophilic infiltrates. There were occasional cryptitis, but no crypt abscess or granuloma was noted.

She received nutritional supplement. No immunosuppressive therapy was started. A repeat EGDS and colonoscopy at 14 mo of age were entirely normal macroscopically. Histologically the colonic architecture was well preserved with minimal lymphoplasmocytic infiltration. A closure of the colostomy was performed at 15 mo of age. Postoperatively she remained well and asymptomatic. The clinical presentation, colonscopic appearance and histologic features were classically that of CD, but the subsequent course, i.e., sustained remission without immunosuppression made a diagnosis of CD unlikely. Hence a diagnosis of IBD-U was made.

**Medical and surgical therapies**

Five of the six patients had immunosuppressive therapies consisted of CS, Aza, cyclosporin and IFX. In addition, one patient (infant No. 1) who had an initial diagnosis of allergic colitis also had elemental diet. All the three patients with CD were given IFX (see above). Three patients required surgery: one had total colectomy, one had colostomy and another had ileostomy.

**Final disease status**

At final review (median duration of follow up: 5.5 years; range 2.0-20 years), all patients survived. Of these, three patients (50%) were in complete remission, two patients with CD had inactive disease with no immunosuppression while one patient with UC was in remission after total colectomy (Table 1). One patient with UC was in remission with Aza. Two patients have active disease despite adequate immunosuppressive therapies at a recommended dose.

**Comparison with patients with later-onset disease**

A comparison was made between the IO-IBD described in the present study and other patients with later-onset IBD (onset of disease after 12 mo of age) who were followed up at the department (Table 2). As compared to patients with later-onset disease, children with IO-IBD were more likely to have bloody diarrhea at presentation (100% vs 55%, P = 0.039) but were not more likely to have an associated autoimmune liver disease (0% vs 19%, P = 0.31), require the use of biologics (50% vs 36%, P = 0.40), or surgery (50% vs 29%, P = 0.27), or achieving remission at final review (50% vs 64%, P = 0.40). However, there was a trend for patients with IO-IBD to discontinue immunosuppressive therapy (50% vs 88%; P = 0.053).

**Comparison with Caucasian patients**

A comparison was made between patients described in the present study and those reported in the literature (Table 3). Three other studies, all from European centers, described IO-IBD.[8,9,14] Generally patients with IO-IBD required aggressive immunosuppression. Between 19% and 33% of the patients had surgery. However, prolonged remission, some without immunosuppression, was achieved in 67% to 100% of patients.

**Mutational analysis**

Mutational analysis for coding regions together with...
splice junctions of \textit{IL10} and \textit{IL10R} were performed by genomic Sanger sequencing of the three patients with CD and one infant with IBD-U. No causative mutation was identified.

**DISCUSSION**

Inherited genetic defect leading to immune dysregulation, the influence of intestinal microbiome and environmental factors have all been considered playing an important role in the pathogenesis of IBD, including IO-IBD\(^{[14]}\). Mutations in \textit{IL10} and \textit{IL10R} have been identified in a subset of infants with severe IO-IBD\(^{[13-16]}\), often presenting with perianal fistulae, respond poorly to medical therapies and needing early surgical interventions\(^{[16]}\). HSCT has been shown to be curative in IBD secondary to \textit{IL10}/\textit{IL10R} deficiency\(^{[13-16]}\).

However, clearly not every young child with IO-IBD have mutations in \textit{IL10} or \textit{IL10R}\(^{[14,15]}\). Of the 13 infants with IO-IBD reported by Begue \textit{et al}\(^{[15]}\), only two (15%) were found to have a deficient \textit{IL10} signaling\(^{[14]}\). Instead the authors found additional compromised signaling in \textit{IL12} in a patient with absent \textit{IL10RB}\(^{[14]}\). Similarly, Shim \textit{et al}\(^{[22]}\) reported that only seven (50%) of the 14 Korean infants with IO-IBD had mutations in \textit{IL10RA}. Thus it is likely that IO-IBD represents a heterogeneous group of disorders with the common feature of early-onset severe colitis within the first weeks to months of life\(^{[8,9,14,22]}\). Mutations in \textit{IL10} and \textit{IL10R} may be responsible in a significant proportion of, but not all, young children with IO-IBD. Uhlig \textit{et al}\(^{[13]}\) have shown that many other monogenic disorders and primary immunodeficiencies, including SCID and Wiskott-Aldrich syndrome, are recognized causes of IO colitis.

In the present study on six Asian children with IO-IBD, the disease phenotype was diverse. From the initial presentation and subsequent disease course, three patients [1 UC (patient No. 2) and 2 CD (patient No. 4 and 5)] closely resembled classical UC and CD. In the remaining three cases, the disease behavior and progression significantly differed from classical CD or UC.

The only patient with IBD-U achieved sustained remission and resolution of the perianal disease after ileostomy was created at four months of age, despite no immunosuppression. The initial features were indistinguishable with that of classical CD with severe perianal abscesses and fistulas, and the presence of deep, linear, extensive ulcerations at the rectum and sigmoid colon. Severe allergic colitis was unlikely as the initial histology showed transmural involvement. There was continuing remission even after the closure of ileostomy at 16 mo of age. Mutational analysis for \textit{IL10} and \textit{IL10R} was negative.

A review in the literature did not reveal any cases of CD with spontaneous remission without immunosuppression or other medical therapy\(^{[31,32]}\). Thus even though the clinical, colonoscopic and histological features in this patient closely resembled that of CD, the disease behavior and progression significantly differed from classical CD or UC.
the child was classified as having IBD-U.

Another interesting case that merits special attention was the child with initial presentation with pancolitis, heavy eosinophilic infiltration of the colonic mucosa, and resistance to elemental formula and even immunosuppression. This closely resembled a case of severe allergic colitis. This was followed at later stage with lymphoplasmacytic infiltration seen typically in IBD. This transformation from allergic colitis to IBD has been similarly observed by other authors[8].

Our findings are similar to those described by other authors[8,9,14]. Generally, patients with IO-IBD need aggressive therapy, often with a combination of immunosuppression[8,9,14]. Some needed biologics such as IFX[8]. Between 19% to 33% needed surgery, either ileostomy or colectomy[8,9]. Nevertheless complete remission can be achieved in a significant proportion of patients either with ongoing immunosuppression or discontinuation of therapy[8,9,14].

With the exception that children with IO-IBD were more likely to have bloody diarrhea at presentation, there were no significant differences between the IO-IBD and children with the onset of disease after one-year of age in terms of developing autoimmune liver disease, the need for biologics, risk for subsequent surgery, achieving remission at final review, or achieving remission without on-going immunosuppression.

Unlike the authors from Korea which showed that 50% of the 14 children with IO-IBD had mutations in IL10RA[19], none of the three patients with CD phenotype and the case with IBD-U in the present study had any identified mutations in IL10 or IL10R. Nevertheless continuing efforts is necessary to identify such mutations in all patients with IO-IBD. However, it should be pointed out that only four of the six patients with IO-IBD had mutational analysis for IL10 and IL10R performed. The remaining two patients, who both had phenotype similar to UC, had no mutational analysis. This was because IO-IBD secondary to mutations in IL10 and IL10R genes usually present with CD phenotype.

The present study was conducted from a region where the incidence of IBD is much lower as compared to the West[33]. This has contributed to the small number of patients with both IO-IBD and later-onset disease reported in the present study.

We did not perform anti-Saccharomyces cerevisiae antibody (ASCA) for the patients with early onset disease. Recently, high ASCA seropositivity rates have been found in patients with early-onset IBD[34]. The implications of finding a positive ASCA in patient with CD include oral involvement and a more severe disease[35]. However, the finding of high seropositivity rate of ASCA in early onset CD has not been reported by other authors[36].

There are several weaknesses in the present study. Firstly, the number of children with infantile colitis described was small. The present study was conducted in an area with low incidence of IBD. Over the study period of 18 years in the only referral center for pediatric IBD in Malaysia, only six cases of IO-IBD were noted. Thus it may be difficult to draw many significant conclusions from the findings of the present study.

Secondly, mutational analysis for other known causes of infantile colitis were not performed in the six cases of IO-IBD described in the present study[10]. Thus we were unable to characterize further the genetic basis of these six cases of IO-IBD described.

In addition, there may be selection bias when comparing the outcome of IO-IBD with the outcome of patients with later-onset disease. It is well known that IO-IBD is a heterogenous group of conditions and is comprised of several different disease caused different genetic mutations but characerized by early onset of disease.

However, it is well known that the incidence of IBD in Asian adults is increasing[33]. It is anticipated that the incidence of IBD in Asian children would similarly be increasing[33]. The present study will add to the body of knowledge for this rare disease in Asian children. Currently, most of the cases of IO-IBD described in the literature were from the Middle East or Caucasian population[8,9].

We conclude that IO-IBD consists of a heterogeneous group of disorders with different pathogenic mechanisms but with the common manifestation of severe colitis presenting in the first few months of life. Aggressive immunosuppression and surgery are often necessary. Nevertheless sustained remission, in some cases without immunosuppression, can be achieved in a significant proportion of patients. Continuing efforts to elucidate novel mechanisms responsible for the breaking down of intestinal integrity is necessary in this group of infants.

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COMMENTS

Background

Inflammatory bowel disease (IBD) is not as common in the Asian population as in the Caucasians, although recent epidemiology studies suggest that the incidence of IBD in the Asian population is increasing. Infantile-onset inflammatory bowel disease (IO-IBD) is uncommon and is usually associated with a genetic mutation. One of the most common mutations described that is associated with IO-IBD is mutations in IL-10 and IL-10 receptor.

Research frontiers

It is important to elucidate the role of IL-10 and IL-10 mutations in children with IO-IBD as it is usually non-responsive to conventional immunosuppressive therapy but may be amendable to stem-cell transplantation.
Innovations and breakthrough

As compared to children with IBD with an onset after the first year of life, IO-IBD achieved remission at a similar rate, were more likely to discontinue immunosuppression therapy while not more likely to require biologics therapy or surgical intervention.

Applications

Although mutations in IL-10 and IL-10R were not found in the present cohort of infantile-onset inflammatory bowel disease, it is important to screen for such mutations in all cases of IO-IBD as the therapy and prognosis is different.

Terminology

IO-IBD refers to a subset of early-onset IBD with an onset before twelve months of life.

Peer-review

The manuscript is interesting and adds new knowledge in the field of IO-IBD but requires a major statistical revision (or no statistical analysis as the conclusions may be false and can not be extrapolated on the bigger group of all IO-IBD patients).

REFERENCES

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