Phenotype of Very-Early-Onset Inflammatory Bowel Disease with Interleukin-10 Receptor A Mutations in 22 Chinese Children

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Abstract

Background: Very-early-onset inflammatory bowel disease (VEO-IBD) with onset in infancy may be caused by genetic mutation. We collected the VEO-IBD patients with interleukin-10 receptor A (IL-10RA) gene mutations to investigate the clinical phenotype and genetic characteristics.

Methods: The data of 22 patients with VEO-IBD with IL-10RA gene mutations were retrospectively analyzed, and high-throughput sequencing was used to identify IL-10RA gene mutations.

Results: All 22 patients in this study had IL-10RA gene mutations, including 4 (18.2%) homozygous mutations and 18 (81.8%) compound heterozygous mutations. Among these mutations, 10 mutations had been previously described and 1 novel mutation was identified. In these patients, c.C301T (p.R101W) (86.4%, 19/22) and c.G537A (p.T179T) (36.4%, 8/22) mutations were the most common mutations. This study showed that the patients had extremely early onset of symptoms, about 81.8% (18/22) of the patients had onset within 1 month after birth, and the onset time was 8.5 (IQR: 3.0–24.0) days. In addition, 77.3% (17/22) of patients had recurrent perianal lesions. Oral ulcers and skin rash were common extra-intestinal manifestations, accounting for 72.7% (16/22) and 63.6% (14/22), respectively. In this study, 3 patients underwent enterostomy and 1 patient experienced intestinal perforation repair. Umbilical cord blood transplantation (UCBT) and thalidomide proved efficacious. Follow-up showed the mortality rate was as high as 45% (9/20).

Conclusions: We should consider the genetic defects in the IL-10 signaling pathway in VEO-IBD patients, particularly when they had early onset of symptoms, perianal lesions and severe colitis.

Background

Inflammatory bowel disease (IBD) refers to a group of non-specific gastrointestinal inflammatory disorders of unknown etiology, encompassing Ulcerative Colitis (UC), Crohn's disease (CD) and undetermined type inflammatory bowel disease (IBD-unclassified). Very early onset IBD (VEO-IBD) is defined as onset of IBD before the age of 6 years and constitutes 4–15% of pediatric IBD patients [1–3], and infantile-onset IBD (IO-IBD) refers to patients less than 2 years of age [4]. Compared with adolescent- and adult-onset IBD, genetic susceptibility plays a greater role in the pathogenesis of VEO-IBD [5]. Recent guidelines and consensus on the diagnosis and treatment of IBD state that children with IO-IBD are at higher risk of underlying primary immunodeficiency [6, 7]. So far, at least 58 susceptibility genes are involved in the pathogenesis of VEO-IBD, including the interleukin-10 (IL-10) and IL-10 receptor (IL-10R) genes mutations which play important roles in VEO-IBD and often accompanied by refractory diarrhea, perianal disease, frequent oral ulcers, skin folliculitis, sepsis, and other conditions [8]. These patients often respond poorly to medical therapy and have a high mortality. We would like to summarize the clinical phenotype, endoscopic–histological, medical therapy and surgical interventions of 22 identified IL10RA gene mutation patients in our hospital, to promote the understanding of this disease and improve the prognosis of children.

Methods

Patients

This study was approved by the Ethics Board at Beijing Children's Hospital, and

informed consent was obtained from each patient's parents. 22 patients diagnosed with VEO-IBD caused by IL10RA gene mutations at Beijing Children's Hospital were enrolled from August 1, 2016, to December 31, 2019. All patients were diagnosed with IBD based on standard tools including clinical features, endoscopy with biopsies, radiology, laboratory testing and genetic testing. The diagnosis of "VEO-IBD" was made according to the Porto criteria and the pediatric Paris modification of the Montreal classification [6,9]. Clinical information was obtained from the medical records and follow-up information, including sex, first symptom and age of onset, clinical features, disease type, disease behavior, disease location, the presence of perianal lesion, family history, medical history, surgical intervention and clinical outcomes. Weight-for -age Z score and height-for-age Z score at initial diagnosis were obtained for each patient by WHO Anthro (version 3.2.2).

Genetic Sequencing

We performed whole-exome sequencing (WES) and Sanger sequencing. Genomic DNA was extracted from peripheral whole blood of patients and their parents using the QIAamp DNA Mini Kit (Qiagen, China). Using the Illumina HiSeq X Ten platform, WES resulted in an average 100×coverage. Targeted sequencing was applied to selected patients.

After sequencing, the original data were saved in FASTQ format. Illumina sequencing adapters and low quality reads (< 80 bp) were filtered by Cutadapt. The Burrows-Wheeler Alignment tool was used to align clean readings with the UCSC hg19 human reference genome. According to previous reports, the bioinformatics pipeline was applied. Briefly, after quality control, the public database was used to filter variants, including Human Gene Mutation Database (HGMD) Professional, and Exome Aggregation Consortium (ExAC), and 1000 genomes, and internal database, and predicted by Mutation Taster, SIFT, PolyPhen-2 and GERP++. The pathogenicity of mutations was evaluated according to the American College of Medical Genetics and Genomics guideline (ACMG). Sanger sequencing was performed using Biosystems 3730 DNA Analyzer and analyzed by Mutation Surveyor V5.0.0 to confirm the causal mutations.

Laboratory Testing, Treatment and Follow-up

The complete blood cell count (white blood cell [WBC] counts, hemoglobin [Hb] platelet count), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and albumin levels, were recorded at the time of the diagnosis. All the patients in this study underwent follow-up for treatment and prognostic

information.

Statistical analysis

Statistics were analyzed using SPSS 22. Continuous data were presented as mean and SD or median and interquartile range (IQR). Categorical variables were reported as frequency and percentage. $P < 0.05$ was considered statistically significant.

Ethical approval

This study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University.

Results

Demographic Features

In this study, 22 children with VEO-IBD were all identified as IL10RA gene mutations, all patients were born in 8 different provinces in northern China and were unrelated. Among the 22 patients, 12 were male and 10 were female, the median age of diagnosis was 170 (IQR: 67.5–473.5) days, consanguineous marriage was denied in all patients. Three patients had a positive family history (13.6%, 3/22).

Genotypes of IL-10RA

All of the 22 patients were identified with IL10RA mutations, and among them, 4 patients (18.2%, 4/22) had homozygous mutations, 18 patients (81.8%, 18/22) had compound heterozygous mutations (Table 1). Altogether, 11 mutant sites were detected in IL10RA. Among the identified IL10RA mutations, 10 mutations had been previously described, including c.C301T (p.R101W), c.G537A (p.T179T), c.349C>T (p.R117C), c.436_437CC>G (P.146fs), c.251C>T (p.T84I), c.493C>T (p.R165X), c.106G>A (p.A36T), c.269T>C (p.L90P), c.299T>G (p.V100G), c.205T>C (p.W69R). 1 novel mutation was identified c.635G>C (p.R212P). Among the patients with IL10RA mutations, c.C301T (p.R101W) (86.4%, 19/22) and c.G537A (p.T179T) (36.4%, 8/22) were the most common mutations. We identified 4 patients (18.2%, 4/22) with same IL10RA p.R101W homozygous mutations, and 6 patients (27.3%, 6/22) had same compound heterozygote IL10RA p.R101W/p. T179T mutations. All patients were born in unrelated families. Parents were heterozygotes for the mutation in all our patients.

Characteristics of the IL10RA Mutations

Among these patients, 81.8% (18/22) of patients had onset of disease within 1 month after birth, all of these patients showed symptoms within 6 months of life, the median age of onset of symptoms, including diarrhea, fever and oral ulcer, was 8.5 (IQR: 3.0–24.0) days. Regarding the first symptoms experienced by the patients, diarrhea, fever and oral ulcers were experienced in 81.8% (18/22), 50% (11/22) and 22.7% (5/22) of patients, respectively. The time of onset of diarrhea, fever and oral ulcers were 6.5(IQR: 2.5-16.0)days, 10(IQR:9.0-19.0) days and 13.4±6.39 days, respectively.

Furthermore, all patients had diarrhea, whereas 68.2% (15/22) patients reported hematochezia and 95.5% (21/22) had fever. 77.3% (17/22) of patients suffered from perianal lesions, including fissure, skin tag, abscess, perianal fistula, rectoperineal fistula, rectovaginal fistula and rectovestibular fistula. Among the 22 patients, perianal abscess was identified in 10 patients (45.5%), perianal fistula was found in 8 (36.4%) patients, 5(22.7%) patients had rectoperineal fistula, 1 patient presented with rectovaginal fistula, and rectovestibular fistula was detected in 1 patient. For other extra-intestinal involvement, 16 patients (72.7%) had skin rash, 1 patient (4.5%) had arthritis, and oral ulcers were experienced by 63.6% (14/22) of the patients.

The average weight-for-age Z score and height-for-age Z score on initial diagnosis were -2.07(IQR: -2.61~-1.78) and -1.74±1.34 respectively.

Laboratory Testing

The patients displayed increased white blood cell counts ($17.21 \times 10^9/L$, [IQR:11.64-19.95]) (reference value: $4-10 \times 10^9/L$), platelet counts ($554.64 \pm 238.54 \times 10^9/L$) (reference value: $100-400 \times 10^9/L$), C-reactive protein ($87.36 \pm 57.39 \text{ mg/L}$) (reference value $< 8 \text{ mg/L}$), and erythrocyte sedimentation rate (23 mm/h, [IQR:9-63.5]) (reference value $< 15 \text{ mm/h}$) and low expression of hemoglobin ($78.5 \pm 11.96 \text{ g/L}$) (reference value: 110-160 g/L), albumin ($24.84 \pm 6.62 \text{ g/L}$) (reference value: 33-55 g/L).

Endoscopic and Pathologic Analysis

In this study, 14 patients underwent gastroscopy and 20 patients received colonoscopy, 2 patients underwent surgery due to intestinal perforation and intestinal necrosis respectively before endoscopy because of their critical condition. Patients showed prominent colonic involvement 95.5%, 21/22, there was no patient had ileocolonic disease. Only 2 patients had gastric ulcer and duodenal ulcer, 1 patient had small bowel involvement. For disease behavior, 16 patients (16/22, 72.7%) had nonstricturing and nonpenetrating disease, 4 patients (4/22, 18.2%) suffered from penetrating disease and 2 patients (2/22, 9.1%) had stricturing disease found on colonoscopy.

Colonoscopy revealed that colonic aphthous and deep ulcers and deep were common (85%, 17/20), and cobblestone change was found in 5 patients (25%, 5/20). Typical histopathological evaluation showed unspecific acute or chronic colitis with multiple ulcerations, crypt structural deformation, cryptitis, and crypt abscess.

Treatment and Prognoses

During this process, all patients received antibiotics. 20 patients (90.9%, 20/22) received enteral nutrition, 13 patients (59.1%, 13/22) were transfused with concentrated red cells and albumin, and 8 patients (36.4%, 8/22) had immune globulin transfusion. 5 patients were treated with steroids, but colonic inflammation persisted despite steroid medication. 4 patients were treated with thalidomide (1.5–2mg/kg. d, adjusted dose according to treatment effect), 1 patient received both infliximab and thalidomide, no adverse effects of thalidomide have been identified in these patients.

4 patients (18.2%, 4/22) had experienced surgery during the course. Among them, 3 patients underwent enterostomy because of intestinal perforation, perianal diseases and intestinal necrosis, intestinal perforation repair was performed in 1 patient. 2 patients underwent umbilical cord blood transplantation (UCBT) in Children's Hospital of Fudan University, Shanghai.

As of April 1, 2020, 2 patients lost to follow-up, 9 patients were dead, the mortality rate was 45% (9/20), and 11 patients (55%, 11/20) were alive. Among the 11 patients, 2 patients remained stable and showed no gastrointestinal symptoms after UCBT, 1 patient achieved sustained clinical remission receiving thalidomide, 2 patients were clinically improved with thalidomide, and clinical improvement was also achieved in 1 patient with exclusive enteral nutrition (EEN). The remaining 5 patients still had recurrent disease activity. None of the patients developed lymphoma.

Discussion

Since the initial report patients with IL10R signaling defects in 2009 by Glocker et al [8], more than 130 VEO-IBD patients with IL-10 or IL-10R gene mutations have been reported [10,11]. Most patients were from Europe and Asian, where IL-10R mutations were more frequent than IL-10 mutations. In this study, we identified 22 VEO-IBD patients with IL10RA gene mutations. In general, VEO-IBD patients with IL-10RA mutations suffered from even more complicated, severe, and intractable disease. They were characterized by very early onset symptoms, common perianal diseases (abscess, fistulas, fissure, skin tag) and extra-intestinal manifestations, such as skin rash and oral ulcers, respond poorly to traditional treatment, and high surgery rate and mortality [11].

In this study, we identified the c.C301T (p.R101W) mutation in exon 3 and the c.G537A (p.T179T) mutation in exon 4 were the most common mutations in the IL10RA gene in Chinese VEO-IBD patients, with a mutation rate of 86.4% and 36.4%, respectively. This was consistent with previous reports from East Asia, but significantly higher than other regions [11-14]. These mutations may disrupt signaling after activation of the IL-10 receptor, and therefore, STAT3 was not phosphorylated and intractable inflammatory responses developed in the gut of pediatric patients [15,16]. In addition, we found that 6 patients (27.3%, 6/22) had same compound heterozygote IL10RA p.R101W/p. T179T mutations, and these patients were born in unrelated families. This was similar to study from China before [17]. In this study, 1 novel mutation of IL-10RA was identified c.635G>C (p.R212P), we did not perform a functional study on this mutation due to conditional constraints. This novel mutant site was not found in HGMD or the other databases and was predicted to be deleterious. Therefore, we speculated that this novel mutation formed a compound heterozygous mutation with the c.C301T (p.R101W) mutation, thereby causing the patient 20 to develop clinical symptoms.

In our study, we did not find mutations in IL10RB or IL10 in our patients, which was consistent with previous reports from East Asia. IL10 RA mutation was more common in East Asian patients than in Western countries, where comparable numbers of IL 10RA and IL 10RB mutation cases exist [18,19]. Furthermore, 81.8% of our patients (18/22) were compound heterozygous mutations, as they were born to unrelated nonconsanguineous families. Which was in contrast to North America and Europe, where the patients were born to consanguineous parents and had homozygous mutations. The high rate of consanguinity in the Arabic population resulted in a high incidence of IL10R homozygous mutations and that associated with the prevalence of VEO-IBD [20]. The genetic architecture of East Asia may be different compared to other regions.

VEO-IBD patients with IL-10RA mutations had extremely early onset of symptoms, all of these patients showed symptoms within 6 months after birth, the median age of onset time was 8.5 days. These patients had refractory diarrhea, hematochezia, fever and growth retardation. In addition, these patients might have recurrent perianal lesions such as abscesses, fistulas, skin tag and fissures, which was consistent with previous researches that patients had extremely early onset of symptoms and multiple perianal lesions [21,22]. In our study, 77.3% (17/22) of our patients suffered from multiple perianal lesions, only 5 patients did not suffer from perianal disease. For extra-intestinal manifestations, oral ulcers and skin rash were very common in these patients, accounting for 72.7% and 63.6%, respectively. Failure to thrive was relatively common in these patients because of the earlier onset, more severe disease course, difficulty in achieving remission, reduced food intake and increased nutritional requirements [23]. In this study, 3 patients had a positive family history that included their siblings dying from similar symptoms.

All the patients in this study were clinically and endoscopically diagnosed with CD. It was interesting to note that VEO-IBD patients with IL-10RA mutations predominantly presented as isolated colitis with deep ulcerations and cobblestone change. However, only 9.1% (2/22) of the patients had upper gastrointestinal or small bowel involvement. This suggested that the colon was particularly prone for immune disorders, which was consistent with other studies involving Turkish and whites [4,18]. Moran CJ et al. reported that the IL-10RA polymorphisms were associated with early-onset UC [24]. These findings suggested that identifying IL-10R mutations may be more important than classifying the disease types (CD or UC) in VEO-IBD patients.

Current therapeutic strategies for pediatric IBD include the use of mesalazine, sulfasalazine, EEN, corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and anti-TNF-antibodies. In this study, the effects of mesalazine, steroids, thalidomide, immunosuppressive agents and biological agents were limited. These were consistent with reports from Western countries [21,25]. In our study, 1 patient achieved sustained clinical remission and 2 patients were clinically improved with thalidomide. This was consistent with Veenbergen S et al. report that thalidomide could promote clinical remission of intestinal symptoms in patients with IL10RA mutation [26]. It was interesting that in our study 1 patient with EEN also achieved clinical improvement, this was consistent with Talya L. Miller et al who described two infants presenting with VEO-IBD achieved clinical remission using EEN [27]. However, thalidomide was currently considered to be a potentially effective treatment for the VEO-IBD patients with IL10RA mutations, but long-term follow-up assessment was still required.

In our study, 2 patients underwent UCBT and remained stable after UCBT. As reported before, Hematopoietic stem cell transplantation (HSCT) was a curative treatment for VEO-IBD patients with IL-10 or IL-10R mutations [11,13]. However, high risks and high costs should be taken into considerations, and long-term follow-up observations were required. Therefore, some patients from our study refused transplantation.

Our results showed that 18.2% (4/22) of the patients had surgical intervention. Due to poor treatment efficacy, some patients with IL-10RA mutations have had to undergo intestinal resection and ileostomy or colostomy [21]. Shim JO et al also reported that patients with IL-10RA mutations were associated with infantile onset, perianal fistulae and early surgical interventions [15].

VEO-IBD patients with IL10RA mutations responded poorly to conventional therapy and had a higher mortality rate. Our study showed a high mortality rate of 45% (9/20). Huang ZH et al reported an overall mortality of 21.4% in patients with IL10RA mutations in China [17]. The study by Mathurin Fumery et al [28] showed that the mortality rate of pediatric CD patients was 0.93%, with a median follow-up time of 11.1 years [IQR, 7.3-15.0]. Despite aggressive treatment, VEO-IBD patients with IL10RA mutations still had a higher mortality rate than pediatric IBD. The high mortality rate in our study was due to severe disease course and several patients gave up treatment.

Conclusions

VEO-IBD patients with IL10RA mutations were phenotypically and genetically distinct from pediatric IBD. We provided the clinical phenotype, endoscopic results, medical therapy, surgical interventions and genetic characteristics of VEO-IBD patients with IL10RA mutations. Therefore, we should consider genetic defects in the IL-10 signaling pathway including IL-10RA in VEO-IBD patients, particularly when they had early onset of symptoms, perianal fistulae and severe colitis.

Abbreviations

VEO-IBD: Very-early-onset inflammatory bowel disease; IL-10RA: interleukin-10 receptor A; UCBT: Umbilical cord blood transplantation; IBD: Inflammatory bowel disease; UC: Ulcerative Colitis; CD: Crohn's disease; IBD-unclassified: undetermined type inflammatory bowel disease; IO-IBD: infantile-onset IBD; WES: whole-exome sequencing; EEN: exclusive enteral nutrition; HSCT: Hematopoietic stem cell transplantation.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Xiwei Xu designed the research and reviewed the paper; Dexiu Guan collected the data and wrote the paper; Jing Zhang and Shu Guo were responsible for follow-up; Feihong Yu, Jin Zhou, Guoli Wang collected and analyzed the data. All authors read and approved the final manuscript.

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Table

Table 1
Summary of Clinical and Genetic Information of very-early-onset inflammatory bowel disease (VEO-IBD) Patients with IL10RA mutations

case	Age of Onset	sex	Fhx	Initial Symptom	Perianal lesion	Extraintestinal Manifestations	Paris Classification	Treatment	Intestinal Surgery	Mutation
1	15d	M	N	Diarrhea	Abscess		A1aL2B3PG1	Thalidomide, UCBT (26 m)	Ileostomy (8 m, perforation)	IL10RA c.301C>T(p.R101W);c.53>A (p.T179T)
2	6d	M	N	Diarrhea, oral ulcer	Perianal fistula	Eczema, oral ulcer	A1aL2B1PG0	EEN		IL10RA c.301C>T(p.R101W);c.53>A (p.T179T)
3	10d	F	N	fever			A1aL1 + 4B1G0		Ileostomy(1 m, Intestinal necrosis)	IL10RA c.349C>T(p.R117C);c.301>T(p.R101W)
4	3d	F	N	Diarrhea, fever, oral ulcer	Abscess, rectoperineal fistula	Eczema, oral ulcer	A1aL2B1PG1	EEN, UCBT (18 m)		IL10RA c.301C>T(p.R101 W); c.301C>T(p.R101 W)
5	1d	M	N	Diarrhea, fever	Perianal fistula	Eczema	A1aL2B1PG1	Corticosteroids, EEN		IL10RA c.537G>(p.T179T); c.301T (p.R101 W)
6	1d	F	Yes, sibling dead (6 m)	Diarrhea	rectoperineal fistula(1m)	Eczema	A1aL2B1PG1	Corticosteroids		IL10RA c.436_437CC>G(P.146fs), c.53>A (p.T179T)
7	5 m	M	Yes, sibling dead (13 m)	Abscess	Abscess, Fissure, Skin tag	Eczema, oral ulcer	A1aL2B3PG1			IL10 RA c.301C>T(p.R101W); c.301C>T(p.R101W)
8	3d	M	N	Diarrhea		Eczema	A1aL2B1G1	Corticosteroids		IL10RA c.301C>T(p.R101 W); c.301C>T(p.R101 W)
9	2 m	F	N	Diarrhea	Fissure, Skin tag,rectoperineal fistula	Eczema, oral ulcer	A1aL2B1PG0	Corticosteroids		IL10 RA c.251C>T(p.T84I);c.493C>T(p.R165X)
10	7d	M	N	Diarrhea, fever		Eczema, oral ulcer	A1aL2B1G0			IL10 RA c.301C>T(p.R101W);c.49>T(p.R165X)
11	6 m	F	N	Diarrhea	Perianal fistula, Skin tag		A1aL2B1PG1	Mesalazine, Corticosteroids, Thalidomide		IL10 RA c.301C>T(p.R101W);c.10>A(p.A36T)
12	6d	M	Yes, sibling dead	Diarrhea, fever	Abscess	Eczema	A1aL2B3PG0			IL10 RA c.269T>p.L90P);c.301C>T(p.R101W)
13	16d	F	N	Diarrhea, fever, oral ulcer		oral ulcer	A1aL2B1G1	EEN		IL10 RA c.299T>G(p.V100G);c.30>T(p.R101W)
14	1d	F	N	Diarrhea, fever	Fissure, abscess, rectoperineal fistula	oral ulcer, skin rash	A1aL2B1PG0			IL10RA c.301C>T(p.R101W);c.53>A (p.T179T)
15	1d	F	N	Diarrhea	Rectovaginal fistula, Perianal fistula	Eczema	A1aL2B1PG0	EEN		IL10RA c.205T>C(p.W69R);c.30>T(p.R101W)
16	22d	M	N	Diarrhea, fever, oral ulcer	Abscess ,Perianal fistula	oral ulcer	A1aL2B1PG0	EEN		IL10RA c.301C>T(p.R101 W), c.301C>T(p.R101 W)

Abbreviations: F, female; M, male; Fhx, family history; N, none; UCBT: umbilical cord blood transplantation. EEN: exclusive enteral nutrition.

case	Age of Onset	sex	Fhx	Initial Symptom	Perianal lesion	Extraintestinal Manifestations	Paris Classification	Treatment	Intestinal Surgery	Mutation
17	8d	F	N	Diarrhea	Rectoperineal fistula, Perianal fistula, Abscess	Eczema, oral ulcer	A1aL2B1PG0		Ileostomy(7m, Rectovaginal fistula, Perianal fistula)	IL10RA c.301C>T(p.R101W);c.537G>A (p.T179T)
18	10d	M	N	Diarrhea, oral ulcer	Abscess	oral ulcer, skin rash	A1aL2B1PG0	EEN		IL10RA c.301C>T(p.R101W);c.537G>A (p.T179T)
19	5d	M	N	Diarrhea, fever		oral ulcer, skin rash	A1aL2B1G1	EEN		IL10RA c.301C>T(p.R101W);c.342G>T (p.R117C)
20	120d	M	N	fever	Perianal fistula, Abscess	Eczema, oral ulcer	A1aL2B1PG1	Thalidomide		IL10RA c.301C>T(p.R101W);c.637G>C (p.R212P)
21	30d	M	N	Perianal fistula	Perianal fistula, Abscess	Eczema, oral ulcer, arthritis	A1aL2 + L4aB3PG0	Infliximab, Thalidomide	Intestinal perforation repair	IL10RA c.537G>A (p.T179T) c.299T>G(p.V100G);
22	9d	F	N	Diarrhea, fever	Rectovestibular fistula	oral ulcer, skin rash	A1aL2B2PG0	Thalidomide, Mesalazine		IL10 RA c.301C>T (p.R101W); c.299T>G (p.V100G)
Abbreviations: F, female; M, male; Fhx, family history; N, none; UCBT: umbilical cord blood transplantation. EEN: exclusive enteral nutrition.										