ABSTRACT

Purpose: A change in diagnosis from ulcerative colitis (UC) to Crohn’s disease (CD) has been reported in pediatric inflammatory bowel disease; however, only a few clinical characteristics and predictors of this diagnostic change have been reported. We aimed to describe the clinical characteristics of patients with UC who underwent a change in diagnosis to CD and identify variables associated with the change.

Methods: The medical records of pediatric patients with UC who were followed up at the National Center for Child Health and Development between 2006 and 2019 were retrospectively reviewed. Clinical data on disease phenotype, laboratory parameters, endoscopic findings, and treatment of patients whose diagnosis changed to CD (cCD) were compared to those of patients whose diagnosis remained UC (rUC).

Results: Among the 111 patients initially diagnosed with UC, 11 (9.9%) patients were subsequently diagnosed with CD during follow-up. There was no significant difference between the cCD and rUC groups in terms of sex, age at initial diagnosis, and the extent and severity of disease at initial diagnosis. Albumin and hemoglobin levels were significantly lower in the cCD group than in the rUC group. The proportion of patients who required biologics was significantly higher in the cCD group than in the rUC group \( (p<0.05) \).

Conclusion: Approximately 10% children initially diagnosed with UC were subsequently diagnosed with CD. Hypoalbuminemia and anemia at initial diagnosis and use of biologics could be predictors of this diagnostic change.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn disease; Pediatric; Diagnosis; Hemoglobins; Albumins; Biologics

INTRODUCTION

Ulcerative colitis (UC) and Crohn’s disease (CD) are chronic inflammatory conditions of the gastrointestinal tract. Differentiating CD from UC is crucial for appropriate medical and surgical management of patients [1,2]. Some children with inflammatory bowel
disease (IBD) do not show the typical endoscopic and histological findings of UC or CD, and up to 30% pediatric patients with IBD are diagnosed with IBD-unclassified (IBDU) [3-12]. The revised Porto criteria, the standardized diagnostic criteria for pediatric IBD, recommend using a combination of clinical symptoms, endoscopic findings, and histological findings for diagnosing IBD [13]. This emphasizes the importance of evaluating the upper gastrointestinal and small bowel regions beyond colonoscopy at initial diagnosis. Moreover, changes in diagnosis during follow-up have been reported in several studies on pediatric patients with IBD due to the development of small intestinal or perianal lesions and detection of epithelioid cell granulomas on histological analysis [3,4,8,9,11,12,14-16]. However, limited studies have revealed the clinical characteristics of patients whose diagnosis changed from UC to CD and the predictors of this diagnostic change. This study aimed to describe the clinical characteristics of pediatric patients whose diagnosis changed from UC to CD and identify the variables that could predict this diagnostic change.

MATERIALS AND METHODS

This study retrospectively reviewed the database and medical records of patients with IBD at the National Center for Child Health and Development (NCCHD), a tertiary children’s hospital in Japan. Patients who were initially diagnosed with UC before the age of 18 years between August 2006 and August 2019 and followed up for >6 months were included in this study. The diagnosis of UC was based on the judgment of experienced physicians who were familiar with the revised Porto criteria [13]. Patients were categorized into two groups. The cCD group included patients whose diagnosis changed from UC to CD during follow-up and the rUC group included patients whose diagnosis remained UC. The Paris classification of the disease phenotype [17], laboratory data, endoscopic findings, and treatment were compared between the cCD and rUC groups. Clinical disease activity was assessed using the Pediatric Ulcerative Colitis Activity Index (PUCAI) [18] or weighted Pediatric Crohn’s Disease Activity Index (wPCDAI) [19]. Remission after diagnostic change was defined as a PUCAI or wPCDAI score of <10.

This study was approved by the Institutional Review Board of the NCCHD (study #2020-017).

Statistical analysis

Continuous variables are described as medians with interquartile ranges, while discrete data are described as percentages. Fisher’s exact test was used to evaluate differences in sex; the extent and severity of disease at initial diagnosis; and use of biologics, tacrolimus, and corticosteroids between the cCD and rUC groups. The Mann–Whitney U-test was used to assess differences in age at initial diagnosis, follow-up duration, and serological parameters between the cCD and rUC groups. Statistical significance was set at p<0.05. All statistical analyses were performed using Stata 15 (College Station, TX, USA) and the EZR software system (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [20].

RESULTS

Among the 111 patients with pediatric-onset UC, 11 (9.9%) were subsequently diagnosed with CD during follow-up. Five patients were initially diagnosed with UC at our center, and six patients were initially diagnosed with UC at the referring hospitals. The clinical features and outcomes of diagnostic change in children with ulcerative colitis are presented in this study.
characteristics of the cCD and rUC groups are shown in Table 1. There was no significant difference between the cCD and rUC groups in terms of sex, age at initial diagnosis, follow-up duration, and the extent and severity of disease at initial diagnosis. However, the proportion of patients who required biologics was significantly higher in the cCD group than in the rUC group ($p<0.05$). The use of corticosteroids ($p=0.061$) was significantly higher in the cCD group than in the rUC group. No extraintestinal manifestations were observed in cCD group. A comparison of laboratory data at initial diagnosis between the cCD and rUC groups is shown in Fig. 1. Albumin and hemoglobin levels were significantly lower in the cCD group than in the rUC group ($p<0.05$). The disease characteristics at diagnosis and clinical course of each patient whose diagnosis changed to CD are summarized in Table 2, including indications for follow-up endoscopic examinations and findings for a definitive CD diagnosis. Capsule endoscopy identified jejunal and ileal ulcerations in all 11 patients. The entire gastrointestinal tract was evaluated when terminal ileal lesions or duodenal lesions were identified on surveillance ileocolonoscopy or when upper gastrointestinal symptoms

![Fig. 1. Laboratory data of the cCD and rUC groups at initial diagnosis.](https://pghn.org)

cCD: patients with ulcerative colitis whose diagnosis changed to Crohn's disease, rUC: patients with ulcerative colitis whose diagnosis remained ulcerative colitis, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Plt: platelet, Alb: albumin, Hb: hemoglobin.

Table 1. Patient characteristics

| Characteristic                  | cCD (n=11) | rUC (n=100) | $p$-value |
|--------------------------------|------------|-------------|-----------|
| Male                           | 5 (45.5)   | 47 (47.0)   | >0.999    |
| Age at initial diagnosis (yr)  | 9 (6–13)   | 11 (0.5–17) | 0.485     |
| Duration of follow up (mo)     | 40 (21–37) | 60 (6–140)  | 0.767     |
| E4 at initial diagnosis        | 9 (81.8)   | 68 (68.0)   | 0.498     |
| S1 at initial diagnosis        | 3 (27.3)   | 24 (24.0)   | 0.727     |
| Biologic use                   | 7 (63.6)   | 32 (32.0)   | 0.048     |
| Tacrolimus use                 | 4 (36.4)   | 17 (17.0)   | 0.215     |
| Corticosteroid use             | 9 (81.8)   | 51 (51.0)   | 0.061     |

Values are presented as number (%) or mean (range). Fisher's exact test, Mann–Whitney test.

cCD: patients with ulcerative colitis whose diagnosis changed to Crohn's disease, rUC: patients with ulcerative colitis whose diagnosis remained ulcerative colitis, E4: pancolitis (proximal to the hepatic flexure) based on the Paris classification, S1: pediatric ulcerative colitis activity index (PUCAI) >65.
### Table 2. Characteristics of inflammatory bowel disease at initial diagnosis and clinical course in patients whose diagnosis changed to CD

| No. | Hospital     | Initial symptoms                                      | Studies performed | Disease extent/Severity | Duration until change in diagnosis (yr) | Findings and manifestations at change in diagnosis to CD | Characteristics of CD at change in diagnosis | Treatment | Disease activity at final visit |
|-----|--------------|-------------------------------------------------------|-------------------|--------------------------|----------------------------------------|----------------------------------------------------------|--------------------------------------------|-----------|------------------------------|
| 1   | NCCHD       | Abdominal pain, diarrhea, bloody stool                | CS/EGD/CE         | E3/S0                    | 2                                      | Surveillance                                              | L3-L4a+L4b                                | 5-ASA     | Remission                    |
| 2   | NCCHD       | Abdominal pain, diarrhea, bloody stool                | CS/EGD/CE         | E4/S0                    | 40                                     | Surveillance                                              | L3-L4a+L4b                                | 5-ASA, PSL | Remission                    |
| 3   | NCCHD       | Diarrhea, bloody stool                                | CS/EGD/CE         | E4/S0                    | 2                                      | Surveillance                                              | J3-L4a                                    | 5-ASA, GLM | Remission                    |
| 4   | NCCHD       | Diarrhea, bloody stool                                | CS/EGD/CE         | E4/S1                    | 60                                     | Relapse of symptoms                                       | L3-L4a+L4b                                | 5-ASA, PSL, AZA, IFX                       | Remission |
| 5   | NCCHD       | Diarrhea, bloody stool                                | CS/EGD/CE         | E4/S0                    | 1                                      | Relapse of symptoms                                       | L3-L4a+L4b                                | 5-ASA, PSL, IFX, AZA, UST                  | Remission |
| 6   | Referring   | N/A                                                   | CS                | E4/S0                    | 10                                     | Relapse of symptoms                                       | L3-L4a                                    | 5-ASA, PSL, AZA, Tac, IFX, GLM            | Remission |
| 7   | Referring   | Diarrhea, bloody stool                                | CS                | E4/S0                    | 4                                      | Surveillance                                              | L2-L4a                                    | 5-ASA, PSL, AZA, IFX, GLM                 | Not remission (PCDAI: 7.5)               |
| 8   | Referring   | Diarrhea, bloody stool                                | CS                | E4/S1                    | 2                                      | Surveillance                                              | L3-L4a+L4b                                | 5-ASA, PSL, AZA, Tac, IFX                 | Remission |
| 9   | Referring   | Diarrhea, bloody stool                                | CS                | E2/S0                    | 7                                      | Surveillance                                              | L3-L4a+L4b                                | 5-ASA for UC                              | Remission |
| 10  | Referring   | Diarrhea, bloody stool                                | CS                | E4/S0                    | 1                                      | Perianal lesion                                            | L3-L4b                                    | 5-ASA, PSL, AZA, Tac, IFX                 | Not remission (PCDAI: 50)               |
| 11  | Referring   | Diarrhea, bloody stool                                | CS                | E4/S1                    | 8                                      | Perianal lesion                                            | L3-L4a+L4b                                | 5-ASA, PSL, AZA, Tac, IFX                 | Remission |

CD: Crohn’s disease, UC: ulcerative colitis, PUCAI: Pediatric Ulcerative Colitis Activity Index, NCCHD: National Center for Child Health and Development, CS: colonoscopy, EGD: esophagogastroduodenoscopy, CE: capsule endoscopy, SBFT: small bowel follow through, E2: left sided ulcerative colitis (distal to the splenic flexure), based on the Paris classification, E3: extensive (distal to the hepatic flexure) based on the Paris classification, E4: pancolitis (proximal to the hepatic flexure) based on the Paris classification, S0: pediatric ulcerative colitis activity index (PUCAI) ≤65, L2: colonic, based on the Paris classification, L3: ileocolonic based on the Paris classification, L4a: upper disease proximal to the ligament of Treitz based on the Paris classification, L4b: upper disease distal to the ligament of Treitz and proximal to the distal third of the ileum based on the Paris classification, B1: non-stricturing and non-penetrating based on the Paris classification, p: perianal disease modifier, based on the Paris classification, 5-ASA: 5-aminosalicylic acid, PSL: prednisolone, AZA: azathioprine, Tac: tacrolimus, ADA: adalimumab, IFX: infliximab, GLM: golimumab, UST: ustekinumab, PCDAI: Pediatric Crohn’s Disease Activity Index.
were present. Endoscopic images of the normal terminal ileum when case 11 was transferred to our center and terminal ileal ulcers during the follow-up were shown in Fig. 2. Although we reviewed the endoscopic images at initial diagnosis in patients whose diagnosis changed to CD, there were no typical CD phenotypes, such as cobblestone appearance or longitudinal ulcers. There were no atypical phenotypes of UC, such as rectal sparing, cecal patch, backwash ileitis, or upper gastrointestinal lesions. However, not all patients in the cCD group underwent esophagogastroduodenoscopy. The histopathological findings at initial diagnosis in the cCD group were consistent with UC based on the revised Porto criteria. None of the patients initially had granulomas; however, granulomas were observed in two patients during follow-up. Five patients were not in clinical remission at the time of the diagnostic change. After the diagnostic change, biologics were introduced or changed in two and three patients, respectively. These changes in management resulted in remission in nine (82%) patients at the final follow-up.

DISCUSSION

This study identified the clinical characteristics of patients whose diagnosis changed from UC to CD in our single-center pediatric IBD cohort. The patients developed atypical manifestations or findings of UC, raising suspicion of CD during follow-up. Re-evaluation led to the diagnostic change to CD and subsequent adjustment of treatment. The extent of UC at initial diagnosis was not significantly different between the cCD and rUC groups. However, hypoalbuminemia and anemia at initial diagnosis and use of biologics during the disease course may be good predictors of the change in diagnosis. In addition, patients whose diagnosis changed to CD appeared to require more intensive treatment during the clinical course; thus, CD should be considered in patients with UC who require intensive management.

Differentiating CD from UC can be challenging, and 6–30% patients with pediatric IBD are diagnosed with IBDU [3-12], which represents a UC-like disease accompanied by features suggestive of CD. Thus, 2–45% patients with UC and IBDU undergo a diagnostic change to CD during follow-up [3,4,8,11,12,15,16]. In a prospective study in Norway, the diagnosis of UC was changed to CD in 14% patients during the 5-year follow-up [3]. However, these previous studies did not describe the clinical characteristics of such patients. Our study showed that approximately 10% patients initially diagnosed with UC underwent a change in diagnosis to CD during follow-up, which is consistent with findings of previous studies. Further, in our study, half of the patients whose diagnosis was changed to CD underwent

Fig. 2. Endoscopic findings of the terminal ileum (case 11). (A) Normal mucosal findings of the terminal ileum on transfer to our institution. (B) Findings of terminal ileal ulcers when perianal lesion appeared.
whole bowel evaluation with small intestinal imaging at initial diagnosis, and their disease extended to the small intestine during follow-up.

In contrast, the upper gastrointestinal tract or the small intestine were not examined at initial diagnosis in the other half of patients, including those with a change in diagnosis after >5 years. We could not determine whether the disease involved the small intestine at the initial diagnosis. Therefore, clinicians should be aware of the possible diagnostic change from UC to CD and consider evaluating the entire gastrointestinal tract at initial diagnosis, as recommended by the revised Porto criteria [13]. At initial diagnosis, there were no atypical UC phenotypes and no findings predictive of change to CD; therefore, the diagnosis could be changed to CD even if initial endoscopic findings are typical of UC. Capsule endoscopy was introduced in our institution in 2013, and all, except one patient, were diagnosed with CD after that. Although gastroduodenal lesions on esophagogastroduodenoscopy or terminal ileal lesions on ileocolonoscopy raise the suspicion of CD, capsule endoscopy appears to be an important diagnostic tool for accurate pediatric IBD diagnosis.

A recently genetic association study and systematic review of the epidemiology, serology, and microbiology of IBD has shown that isolated colonic CD could be an intermediate between ileal CD and UC [21,22]. The Pediatric IBD Porto group have developed new criteria, the “PIBD-Classes,” to differentiate pediatric IBD into five categories to standardize the classification of subtypes—typical UC, atypical UC, IBDU, colonic CD, and CD [23-25]. Evaluation of the entire gastrointestinal tract has become more important, and recent advances in imaging studies and endoscopic devices can help clinicians in examining the small intestine [26-28]. In our study, four of five patients who had not achieved clinical remission at the time of diagnosis achieved it after the diagnostic change by optimizing CD treatment, including switching one biologic to another. Thus, changing the diagnosis can lead to a better prognosis. With the emergence of new biologics for IBD [29-32], appropriate classification of IBD is crucial for medical management and clinical trials.

A few studies have identified the predictors of the diagnostic change from UC to CD at initial diagnosis. Melmed et al. [33] have shown that initial presentation with non-bloody diarrhea, weight loss ≥10%, and greater disease extent at initial colonoscopy can predict the diagnostic change in adults with IBD. In our study, not all initial symptoms could be investigated due to missing data in some medical records of patients, especially those of patients diagnosed at referring hospitals. In our study, there was no significant difference in the proportion of patients with pancolitis between the cCD and rUC groups. One of the reasons for this discrepancy between previous studies and ours may be that pancolitis at initial diagnosis is more common in pediatric patients with UC than in adult patients [34]. In addition, a higher frequency of use of biologics has been reported for CD than for UC [35], which is consistent with our findings.

Laboratory parameters have not been established as predictors of the diagnostic change from UC to CD. However, the trends of some parameters in pediatric patients with IBD have been reported to differ between UC and CD at initial diagnosis. Patients with CD have lower albumin and hemoglobin levels and higher erythrocyte sedimentation rates, C-reactive protein levels, and platelet counts than those with UC [36-39]. In our study, laboratory parameters were compared between the cCD and rUC groups. Hypoalbuminemia and anemia at initial diagnosis were associated with a future change in diagnosis from UC to CD in pediatric patients. This result is similar to the findings of a previous study, which
reported that hypoalbuminemia could be a predictor of the diagnostic change from IBDU to CD [12]. Other studies have emphasized that differences in laboratory parameters could be affected by the distribution and severity of disease [37,39]. Mack et al. [38] have reported that patients with colon-only CD are more likely to show normal laboratory parameters than those with CD involving the small intestine or the upper gastrointestinal tract. In our study, no significant differences were observed between the rUC and cCD groups in terms of erythrocyte sedimentation rates, platelet counts, and C-reactive protein levels, possibly because the disease severity at initial diagnosis was similar between groups. Although further studies to analyze these laboratory parameters according to disease location, disease severity, age at onset, and duration from onset to diagnosis are required for more precise evaluation, a change in diagnosis should be considered for children with UC who present with hypoalbuminemia and anemia.

The limitations of this study are its retrospective nature and inclusion of a relatively small number of patients from a single institution. Individualized endoscopy timing may have led to a selection bias. The mode of diagnosis and follow-up evaluation cannot be standardized because of the retrospective nature of the study. Furthermore, the follow-up duration varied between patients, and a longer follow-up period could have identified more patients with UC whose diagnosis changed to CD. We did not determine the precise diagnostic criteria for IBDU; therefore, the cCD group may have included patients with IBDU, particularly those with incomplete data on initial diagnostic workups. Despite these limitations, the findings of our study are valuable to identify pediatric patients with UC whose diagnosis needs to be carefully re-evaluated as appropriate diagnosis can lead to better outcomes for vulnerable pediatric patients with IBD. A multicenter prospective study with a longer follow-up period should be conducted to determine the potential need for the diagnostic change from UC to CD.

In conclusion, a possible change in diagnosis from UC to CD in pediatric patients with IBD should be considered, particularly for patients who initially present with hypoalbuminemia and anemia. Extensive examination of the entire gastrointestinal tract at initial diagnosis and periodic re-evaluation during follow-up for patients with UC is essential for accurate diagnosis and effective management with better outcomes.

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