Clinical Case Report

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Inflammatory bowel diseases: a burden in pediatrics

Case series and a review of the literature

Cristina Oana Mărginean, MD, PhD[a], Lorena Elena Meliţ, MD, PhD[a,*], Simona Mocanu, MD, PhD[b], Maria Oana Mărginean, Student[a]

Abstract

Introduction: Inflammatory bowel disease is a chronic condition of the gastrointestinal tract, comprising mainly Crohn disease (CD) and ulcerative colitis (UC). Both of them are frequently encountered in children, being multifactorial conditions, with an unclear etiology.

Patients concerns: We present 4 cases of inflammatory bowel disease (IBD) in children in order to underline the variable evolution depending on the patient's particularities.

Diagnosis, Interventions & Outcomes: The first case, a 13-year-old male patient, with a history of Henoch–Schonlein purpura, was admitted for rectal bleeding and weight loss, with normal laboratory parameters. The colonoscopy and the histopathological examination established the diagnosis of UC. The evolution was initially favorable under corticosteroids and sulfasalazine, but with 3 relapses in 2 years. The second case, a 16-year-old male patient, with a history of lactose intolerance and constipation, was admitted for bloody, diarrheic stools, the laboratory tests pointing out only leukocytosis with neutrophilia. The colonoscopy and histopathological examination established the diagnosis of UC. The patient's evolution was slowly favorable. The third case, a 9-year old male patient, with emotional disorders and babbling, admitted for semiconsistent, bloody stools, with increased inflammatory tests, whose colonoscopy pointed out diffuse edema and hemorrhages, the histopathological examination establishing the diagnosis of CD. The evolution was initially favorable, but with 5 relapses in 3 years. The last case, a 12-year-old male patient, was admitted with diarrheic, bloody stools, refractory to antibiotics, and weight loss, with increased inflammatory tests. The colonoscopy pointed out ulcerations, hemorrhages, and disseminated puss deposits. The histopathological examination established the diagnosis of CD. The patient's evolution was favorable, with only 1 relapse in 3 years.

Conclusions: The adequate management, especially the self-management can influence the prognosis of patients with IBD, even though it is unpredictable and burdened by the risk of malignant transformation.

Abbreviations: CBC = complete blood count, CD = Crohn disease, Hb = hemoglobin, IBD = inflammatory bowel disease, Leu = leukocyte, Neu = neutrophilia, PLT = platelets, UC = ulcerative colitis, W = weight.

Keywords: Crohn' disease, inflammatory bowel disease, pediatric patients, ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract, comprising mainly Crohn disease (CD) and ulcerative colitis (UC). Even though the incidence rates present a wide variability in children, it seems that it is one of the most common gastrointestinal diseases affecting children in the developed countries.[1] Even though the real incidence of these 2 gastrointestinal conditions is uncertain, it seems that CD presents a diagnostic annual rate in children between 0.2 and 8.5 per 100,000 individuals, while UC is encountered at a rate between 0.5 and 4.3 per 100,000.[2,3] The etiology of IBD is not fully understood, being a multifactorial disease. The pathological mechanism of IBD consists in a dysregulation of the immune interaction concerning the relationship between enteric antigens and the enteral mucosa leading to a chronic, immune-mediated inflammation.[4–6] The patients with IBD can present different gastrointestinal symptoms at presentation with a variable severity, including abdominal pain, diarrhea, gastrointestinal bleeding, intestinal fistula, intra-abdominal abscess, or perianal disease.[4] In comparison to the onset of IBD with different gastrointestinal patients, certain patients can present an atypical onset with extraintestinal manifestations involving different systems or organs, such as musculoskeletal system, skin, hepatobiliary, and ocular systems.[7]

The diagnosis of IBD is mainly based on the patient's history, the macroscopic aspect of the mucosa at colonoscopy, and the histopathological examination. The patient's history must focus especially on recent travels, antibiotics treatment, the presence of allergic manifestations, and the variability of the symptoms being possibly related to the ingestion of different aliments. The family

Editor: Johannes Mayr.

The authors report no conflicts of interest.

[a] Department of Pediatrics I, University of Medicine and Pharmacy, [b] Department of Pathology, County Hospital, Tîrgu Mures, Romania.

[*] Correspondence: Lorena Elena Meliţ, Department of Pediatrics I, University of Medicine and Pharmacy Tirgu Mures, 38 Gh. Marinescu St., 540139 Tîrgu Mures, Romania (e-mail: lory_chimista89@yahoo.com).

Medicine (2017) 96:11(e6329)

Received: 29 December 2016 / Received in final form: 16 February 2017 / Accepted: 16 February 2017

http://dx.doi.org/10.1097/MD.0000000000006329

history is also important due to the fact that it can reveal similar symptoms or other specific symptoms for IBD in another family member. The macroscopic aspect encountered at colonoscopy can be specific for UC because it will always involve the rectum, being possible to extend proximally.[2] On the contrary, CD can affect any portion of the gastrointestinal tract, with healthy area in between.[2] The colonoscopy also provides the possibility of taking biopsies in order to differentiate CD from UC, when the disease affects the descending colon. Other diagnostic methods, such as abdominal ultrasound, barium enema, upper gastrointestinal barium examination, computed tomography (CT), endoscopic capsule, or laboratory tests [complete blood count (CBC) count, C-reactive protein, erythrocyte sedimentation rate, calprotectin, etc], can also be used as diagnostic tools, but the diagnosis will be confirmed only by colonoscopy and histopathological examination from the biopsy specimens.[2]

The management of IBD involves medical or surgical treatment. The medical management includes multiple drug agents, such as corticosteroids for 4 to 6 weeks, which are very effective in inducing remission, but not in maintaining it; immunomodulators, such as azathioprine and 6-mercaptopurine, used to maintain remission; 5-aminosalocylic acid agents, such as sulfasalazine and mesalamine; and biological therapy for refractory cases to any other of the above mentioned therapies.[2] Surgical treatment is used in both CD and UC, for treating the potential complications, such as perforation, fistulae, toxic megacolon, abscesses, stricture, or even malignancy.[2]

Informed consent was obtained from the patient's mothers (legal guardians) for publication of these 4 case reports.

2. Case series

2.1. Case 1

2.1.1. Presenting concerns. We present you the case of a 13-year-old male patient, admitted in our clinic for inferior digestive hemorrhage, semiconsistent, bloody stools for approximately 3 weeks, tenesmus, and weight loss (approximately 3 kilos in the last month). The personal history revealed an episode of Henoch–Schonlein purpura 1 year before the present admission.

2.1.2. Clinical findings. The clinical examination at the moment of admission showed only diffuse abdominal pain at superficial and deep palpation.

2.1.3. Diagnostic focus and assessment. The laboratory tests, such as CBC count, C-reactive protein, erythrocyte sedimentation rate, transaminases, urea, creatinine, stool culture, and stool examination for ova and parasites, were all in normal limits. The patient was also tested for *Clostridium difficile* infection, but the result was negative. We performed a colonoscopy, and we identified multiple ulcerations, hemorrhagic lesions, and pus deposits of the rectal mucosa, the descending and transverse colon presenting a normal macroscopic aspect. Therefore, we raised the suspicion of an UC (Figs. 1 and 2). We also took multiple biopsies of both, the normal and pathological areas, and the histopathological examination established the diagnosis of colitis with activity signs. On the basis of all mentioned above, we interpreted the case as UC.

2.1.4. Therapeutic focus and assessment. We administered treatment with intravenous steroids and antibiotics for 5 days with a favorable evolution. The patient was discharged with the recommendation to continue the steroids orally for approximately a month with taper after 2 weeks, associated with not only potassium, proton pump inhibitors, and calcium supplements, but also long-term sulfasalazine therapy and probiotics.

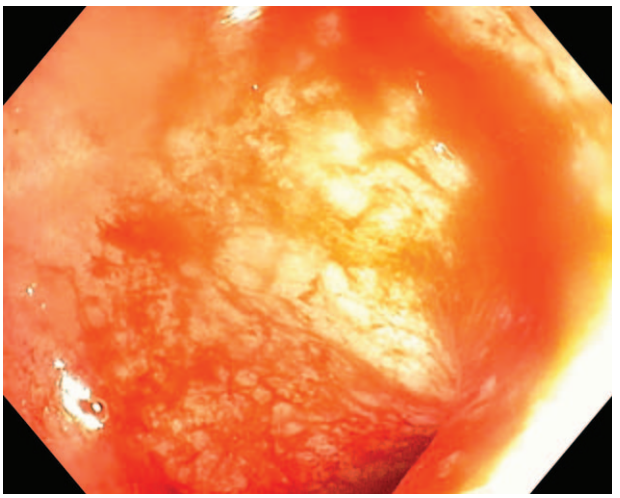

Figure 1. Endoscopic aspect of the rectal-anal junction mucosa with microulcerations, bleeding, and pus (first case).

2.1.5. Follow-up and outcome. The evolution of the patient was favorable initially, but in the following 2 years after the diagnosis, he presented 3 relapses, all in context of psychoemotional school-related stress. These flares solved with short-term steroids therapy, and he is now only on treatment with sulfasalazine. The prognosis depends on the number of relapses and on the patient's education and skills to recognize the first symptoms of a relapse.

2.2. Case 2

2.2.1. Presenting concerns. The second case describes a 16-year-old male patient admitted in our clinic for bloody, diarrheic stools for approximately 3 to 4 weeks associated with tenesmus. The patient presented a personal history of lactose intolerance and constipation during infancy. We must also mention that the symptomatology appeared under stressful conditions, poor adjustment to school change.

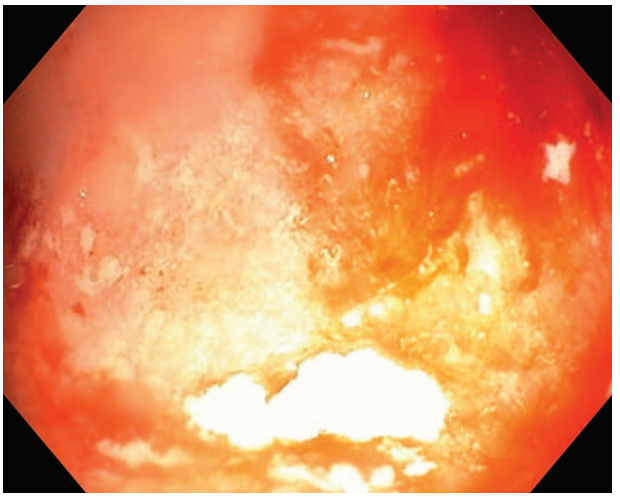

Figure 2. Endoscopic aspect of the rectal mucosa with microulcerations, bleeding, and pus (first case).

2.2.2. Clinical findings. The clinical examination performed at the moment of admission did not reveal any pathological elements.

2.2.3. Diagnostic focus and assessment. The CBC showed leukocytosis with neutrophilia, but the erythrocyte sedimentation rate and C-reactive protein were in normal limits. The other laboratory tests, including transaminases, urea, creatinine, stool culture, and stool examination for ova and parasites, were all in normal limits. The test for *C. difficile* infection was also negative. The colonoscopy revealed multiple ulcerative and hemorrhagic lesions of the sigmoid and rectal mucosa, with a normal macroscopic aspect of the colonic mucosa in rest (Figs. 3 and 4). These modifications were suggestive for an UC; therefore, we took seriate biopsies from the rectal, sigmoid, and the descending colon mucosa. The histopathological examination established the diagnosis of chronic colitis with activity signs. Thus, our final diagnosis was of UC.

2.2.4. Therapeutic focus and assessment. We initiated treatment with oral treatment with steroids and antibiotics for 5 days. The patient's evolution was mildly favorable during admission, with the persistence of bloody, diarrheic stools, but in a less amount when compared with the moment of admission. At discharge, we recommended the continuation of oral steroids for approximately 1 month with progressive withdrawal after 2 weeks, associated with not only potassium, proton pump inhibitors, and calcium supplements, but also long-term therapy with sulfasalazine and probiotics for a month.

2.2.5. Follow-up and outcome. The patient's evolution was unfavorable once he started the taper of steroids, with the reappearance of bloody stools in a greater amount; therefore, we were forced to reinitiate the initial dose of steroids, and maintain it for another 2 weeks, also continuing the sulfasalazine. The afterwards evolution was favorable, even after the taper of steroids treatment. In the following 3 months, the patient did not present any relapse. The prognosis of this patient depends, as in the previous case, on the number of relapses, his education, and self-management of his condition.

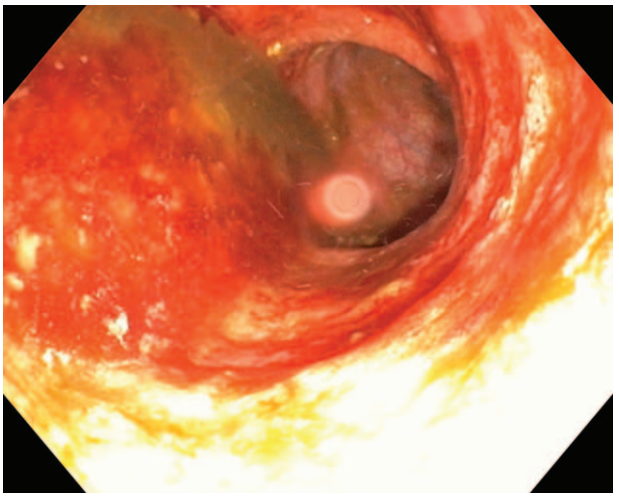

Figure 3. Multiple ulcerations and hemorrhagic lesions of the rectal mucosa—endoscopic aspect (second case).

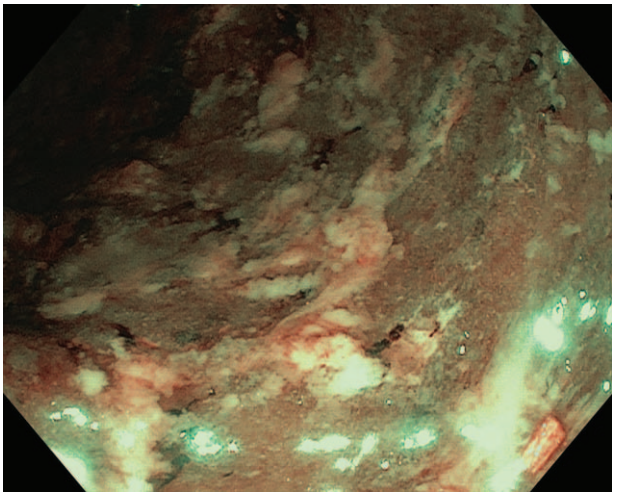

Figure 4. Narrow band imaging (NBI)—endoscopic aspect of sigmoid mucosa with ulcerations and hemorrhagic lesions (second case).

2.3. Case 3

2.3.1. Presenting concerns. Our third case is about a 9-year-old male child, admitted in our clinic presenting 1 episode of vomiting and 1 semiconsistent stool per day for approximately 2 months, massive weight loss (approximately 10 kg in the last 2 months, fatigability, adynamia, recurrent abdominal pain, increased liquid intake, fever (39°C in the evening) for approximately 3 days.

2.3.2. Clinical findings. The clinical examination at the moment of admission revealed reduced general status, ailing face, pale, dry skin, mild bilateral edemas of the inferior limbs, and abdominal bloating with discrete diffuse tenderness at palpation, body weight: 25 kg. We also noticed that the child was emotionally disabled, with behavioral disorders and speech impediment.

2.3.3. Diagnostic focus and assessment. The laboratory test revealed a mildly increased level of erythrocyte sedimentation rate (29 mm/h), elevated C-reactive protein (25 mg/L), iron deficiency (5.71 μmol/L), and hypoproteinemia (5.47 g/dL). We also investigated anti-transglutaminase and anti-endomysial antibodies, but they were within normal limits. The stool examination showed the presence of leukocytes, and a pH of 5.5, without any other pathological elements. Both the stool culture and the test for *C. difficile* infection were negative. Due to his emotional disorders, we requested a neuro-psychiatry consult and a psychological examination, which established the diagnosis of emotional, talking, and behavioral disorders recommending psychological counseling. Abdominal ultrasound and upper gastrointestinal barium contrast study were without pathological findings. The esophagogastroduodenoscopy and the biopsies from the esophagus, stomach, and duodenum were normal. The colonoscopy revealed a follicular aspect of the mucosa with edema (Figs. 5 and 6). The histopathological examination of the colonic mucosa confirmed the diagnosis of CD.

2.3.4. Therapeutic focus and assessment. We initiated long-term *treatment* with sulfasalazine and probiotics for 1 month discharging the patient in a good general status after 1 week.

2.3.5. Follow-up and outcome. The evolution of the patient was burdened by 5 relapses in the following 2 years after diagnosis, with favorable evolution after the administration of

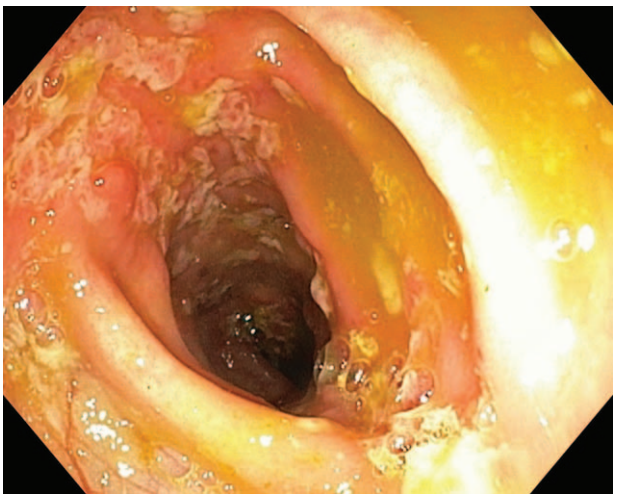

Figure 5. Descendent colonic mucosa with micronodules, ulcerations, and lining denudation—endoscopic aspect at the last relapse (third case).

short-term intravenous steroids and antibiotic therapy. At the moment of the third relapse, we also decided to initiate long-term treatment with azathioprine. The prognosis will depend mainly not only on the number of future relapses and on the ability of the patient to recognize the specific symptoms of a relapse in order to administer as early as possible an adequate treatment, but also on the patient's self-control in order to manage adequately his emotional disorders.

2.4. Case 4

2.4.1. Presenting concerns. The last case we present is about a 12-year-old male patient, admitted to our clinic with the following complaints: diarrheic stools with fresh blood, abdominal pain, and fever for approximately 2 weeks. The patient was initially admitted in the regional hospital with the suspicion of an acute enterocolitis, where he received antibiotics and symptomatic treatment, but without any improvement of symptomatology. He was referred to our clinic for further treatment. The patient had lost 4 kg of his body weight during the hospital stay in the regional hospital.

2.4.2. Clinical findings. The clinical examination at the moment of admission revealed reduced general status, pale skin, diminished cutaneous turgor, and diffuse abdominal tenderness at palpation. His body weight was 26.8 kg at admission to our hospital.

2.4.3. Diagnostic focus and assessment. The laboratory tests performed on the day of admission showed increased inflammatory biomarkers: erythrocyte sedimentation rate of 41 mm/h and C-reactive protein of 15.73 mg/L. The CBC count pointed out leukocytosis (Leu 16 140/mm^3) with neutrophilia (Neu 11 290/mm^3), thrombocytosis (PLT 630 000/mm^3), and also anemia (Hb 9 g/L). We encountered a decreased level of iron and hypocalcemia. The stool culture and *C. difficile* infection examination were negative. The abdominal ultrasound revealed abdominal bloating, and the upper gastrointestinal barium radiological examination was normal. We performed an esophagogastroduodenoscopy taking seriate biopsies from the esophagus, stomach, and duodenum, but they were all normal. The colonoscopy pointed out multiple ulcerations and hemorrhages of the colonic mucosa with a hematoma at the level of rectum (Figs. 7 and 8). The histopathological examination established the diagnosis of CD.

2.4.4. Therapeutic focus and assessment. We administered intravenous steroids and antibiotics for 7 days with favorable evolution. We discharged the patient with the recommendation to continue the steroids orally for approximately 1 month, associated with long-term sulfasalazine therapy.

2.4.5. Follow-up and outcome. The evolution was relatively favorable during the next 2 years; the patient suffered 1 relapse with favorable evolution after a short-term oral steroid therapy, continuing the therapy with sulfasalazine.

3. Discussion

IBD can occur at any age. According to the age at onset, IBD can be classified into pediatric onset (<17 years), early onset (<10 years), very early onset (<6 years), infant/toddler onset (0–2 years), and

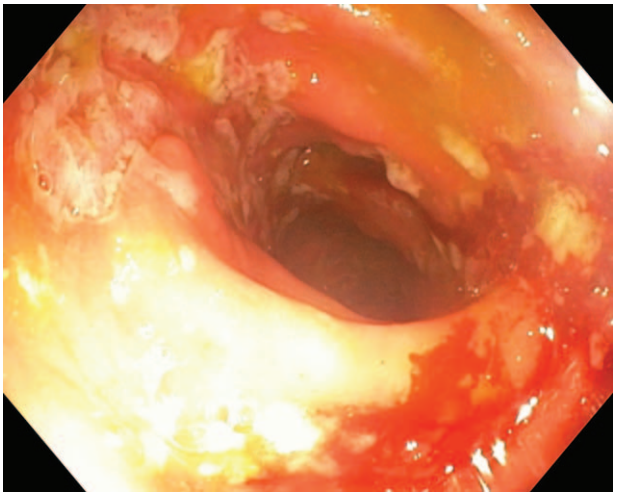

Figure 6. Descendent colonic mucosa with follicular and hemorrhagic aspect—endoscopic aspect at the last relapse (third case).

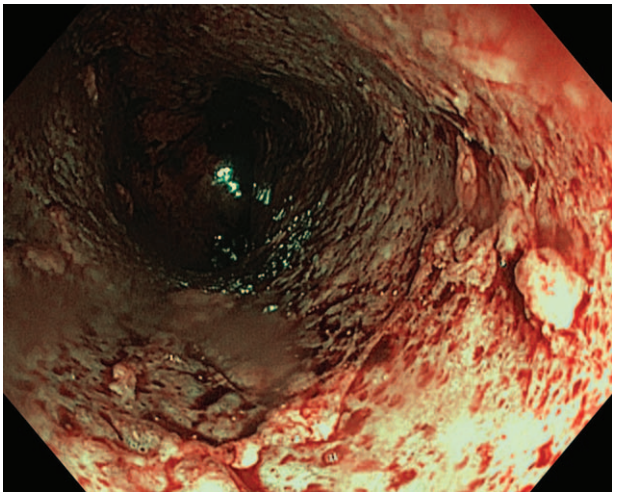

Figure 7. Narrow band imaging (NBI)—endoscopic aspect of the colonic mucosa at the moment of diagnosis—ulcerations (fourth case).

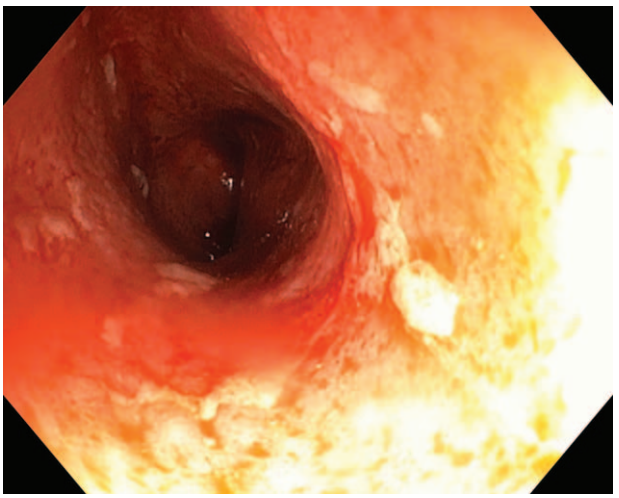

Figure 8. Descendent colonic mucosa with ulcerations, bleeding—endoscopic aspect at the moment of diagnosis (fourth case).

neonatal onset.[8] Three of our patients, both with UC and 1 with CD presented a pediatric onset of the disease, while 1 with CD presented an early onset. Recent epidemiological studies suggest an increasing incidence of IBD in both adults and children,[9,10] with a higher prevalence of UC in Europe, while CD is more frequently encountered in Australia, and a lower overall prevalence of both conditions in both Mediterranean and Eastern European countries.[11] CD seems to affect predominantly females during late adolescence and early adulthood, while at younger ages, the disease tends to affect predominantly males.[11] Similarly, both cases of CD presented above were boys, a 9-year-old patient, and a 12-year old patient, respectively.

Inflammatory biomarkers, such as C-reactive protein, have been reported to be elevated in a substantial proportion of asymptomatic pediatric patients diagnosed with IBD.[12] In adult patients with IBD, a discrepancy between symptoms and biochemical markers of inflammation was reported. However, in pediatric patients, the data are contradictory.[13–15] Therefore, C-reactive protein is one of the inflammatory biomarkers used as surrogate markers of endoscopic IBD activity mainly due to the increased cost and low accessibility of endoscopy for monitoring disease activity.[15] Nevertheless, C-reactive protein seems to be less accurate for patients diagnosed with UC in comparison to those with CD, a fact that can be explained by the limitation of inflammation to the mucosa in UC, in comparison to the transmural inflammation pattern in CD.[16] We found that C-reactive protein was in normal ranges in both our patients with UC at the time of diagnosis, even though the clinical symptoms were much more severe than in the 2 patients diagnosed with CD, where C-reactive protein was encountered to be elevated. The gold standard in the assessment and monitoring of IBD remains upper and lower endoscopy with seriate biopsies.[17]

The clinical course of IBD and the management itself represent a great burden for the patient, especially for the pediatric group. For example, approximately 10% of patients diagnosed with UC need hospitalization due to the severity of symptoms.[18] In the 2 cases of UC presented by us, the patients required hospitalization, 1 of them receiving corticosteroids orally, and the other one intravenously, and both of them continued corticosteroid treatment orally. Both patients presented initially a favorable evolution, but the patient who received only oral treatment with corticosteroids presented with reappearance of symptoms once he started to decrease the dose, therefore needing a longer corticosteroid administration, of approximately 6 weeks. Even though corticosteroids are used for the treatment of IBD relapse, 5-aminosalicylic acid and sulfasalazine are used as maintenance therapy. In certain cases, the patient's evolution requires the administration of immunomodulators or even biological therapy. Only 1 of our 4 patients needed the initiation of immunomodulation therapy, receiving long-term azathioprine treatment. Usually, children presenting diarrhea, abdominal pain, and bloody stools are mistakenly diagnosed with infectious diarrhea leading to a delay in establishing the correct diagnosis.[19] Only 1 of our patients, patient 4 was initially mistaken to present an infectious diarrhea, being finally diagnosed with CD, but fortunately the diagnosis was delayed only for approximately 3 weeks. Regarding the other 3 patients, the delay in diagnosis was caused by their lack of awareness and by the fact that they did not present to a doctor at the moment of their first symptoms. The most frequent signs and symptoms encountered in patients with IBD are gastrointestinal symptoms such as abdominal pain, diarrhea, gastrointestinal bleeding, intestinal fistula, intra-abdominal abscess, or perianal disease.[4] In a study performed on Chinese pediatric patients with IBD, the most frequent clinical manifestations were diarrhea in patients with UC, and abdominal pain in patient with CD.[19] All 4 patients diagnosed by us with IBD presented a typical onset of the disease with gastrointestinal symptoms, such as diarrhea, abdominal pain, and rectal bleeding, without any extraintestinal manifestation. It is well known the fact that CD can affect any part of the gastrointestinal tract. Thus, the same study mentioned above found an incidence rate of CD involving the esophagus, stomach, and duodenum of 63%.[19] Both our patients with CD presented only colonic involvement. Also, the mean age at the time of diagnosis was 10.4 years in patients with UC and 10.1 years in patients with CD.[19] Similarly, our patients with CD were diagnosed before adolescence, at the age of 9 and 12 years, respectively. In contrast, both patients with UC were diagnosed during early and late adolescence, at 13 and 16 years, respectively.

Emotional disorders are more frequently encountered in patients with IBD, being related not only to the onset of the disease but also to the relapses. Two recent studies showed that adolescents' well-being, emotional and social functioning, body image, or poor college adjustment are related to an increased disease activity.[20,21] The first of our patients diagnosed with UC was reported to have school-related stressful conditions at the moment of every relapse. The second patient diagnosed with UC presented the same stressful events at the moment of diagnosis. The first patient with CD was also diagnosed with emotional disorders and babbling. Only the last patient presented no emotional disorders associated, and related or not to this fact, he is the one that presented the most favorable evolution of all 4 patients.

Diet can represent a trigger or a therapy for IBD. For example, it seems that diets high in animal fats and low in fruits and vegetables are associated with an increased risk of IBD, while defined formula diets and supplementation of vitamin D improve the outcome in children with IBD by reducing the inflammation and dysbiosis, and by increasing the efficacy of IBD therapy.[22] Also, an innovative trend in the management of patients with IBD is represented by fecal microbiota transplantation, designed to correct dysbiosis in this group of patients. Nevertheless, Kumagai et al[23] described a case of a 3-year-old child with severe refractory UC in which fecal microbiota transplantation has failed in improving the outcome. A current innovative approach of pediatric patients diagnosed with IBD is related to the self-management of their condition. Therefore,

there were defined interventions and group supports in order to enhance the ability of these patients to manage their condition and to self-controlling it by recognizing the early symptoms of a relapse.[24]

The aspect regarding the symptoms and diagnosis is very similar both in children and adults, but the evolution can be very different. The age is an essential factor that can influence the prognosis of IBD due to the fact that as smaller the onset age is, the higher the amount of complications will be. Without taking into consideration this unchangeable fact that can lead to a worse prognosis in children compared with adults, adults' awareness regarding their conditions is without doubt higher, even though medication nonadherence is encountered more frequently in adults.[25] Adults own a more developed ability to recognize the symptoms of a relapse and to present sooner to their gastroenterologist than children who are afraid to confess their symptoms and are not aware of the risks of their condition. The diagnosis of a chronic condition such as IBD will present a negative impact on the quality of life at any age, but it seems this impact is more pronounced at a younger age.[26] Therefore, educational interventions might be helpful in the management of all patients diagnosed with IBD independently of age.

The prognosis of both CD and UC is burdened by the well-documented risk of colon cancer depending among other on the age at the time of diagnosis. For both conditions, the risk of malignant transformation is higher when the age at diagnosis is younger.[2]

The factors that can influence the outcome of IBD involve mainly not only the patient's awareness of his chronic condition, his ability to recognize the early symptoms of a relapse, and his willingness to present as soon as possible to his gastroenterologist in order to benefit from the medical intervention, but also his compliance regarding the chronic treatment between relapses. Even though we presented only 4 cases with IBDs, they all involved children and were designed to reveal the differences between these cases regarding the symptoms, the diagnosis and evolution depending on the individual characteristics, such as age at onset, behavior, emotional, and psychological features.

4. Conclusions

UC and CD remain 2 unpredictable chronic conditions in children. The evolution of these 2 conditions depends mainly on the number of relapses, but it also depends on the patient's emotional status and his ability to develop a proper self-management of the disease. Therefore, the medical approach of a pediatric patient with IBD should involve also a neurologist and a psychiatrist in order to improve the outcome. Also, educational interventions and medical and psychological support for these groups of patients could present a major positive impact on their quality of life.

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