DIFFUSE GIANT INFLAMMATORY POLYPOSIS AT THE ONSET OF ULCERATIVE COLITIS, PRESENTING WITH PROTEIN-LOSING ENTEROPATHY AND MASQUERADING AS INTESTINAL INTUSSUSCEPTION

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Abstract

Inflammatory polyposis (IP) in ulcerative colitis (UC) appears most often over the course of the disease, being very rarely described as a presenting feature. Giant IP (> 1.5 cm in diameter or length) is very uncommon and most reported cases have had a localized form. We report a case of a male teenager, who was admitted in our clinic after 16 days of abdominal pain and bloody diarrhea. He was found with palpable abdominal mass, protein-losing enteropathy and anemia. Intestinal intussusception was considered in the surgical department; however, laparotomy did not reveal any abnormality. Readmitted to our department two months later, he was diagnosed by colonoscopy and histology with giant diffuse IP and moderate-to-severe ulcerative pancolitis. Therapy with Mesalazine and Prednisone led one month later to histological remission of the UC and reduction in the number and size of the polyps. Being a steroid-dependant UC, Azathioprine was added 3 months later and he has remained in microscopical remission since (5.6 years later). We discuss our case in relation to the literature and we emphasize the importance of mucosal healing, given also the high risk of colorectal cancer. To the best of our knowledge, this is the first case of pediatric UC presenting with giant diffuse IP at the disease onset.

Key words: giant inflammatory polyposis, ulcerative colitis, onset, protein-losing enteropathy, children

Introduction

Inflammatory polyps (or "pseudopolyps") arise during the process of regeneration and healing of the ulcerations, in 12.5-20% patients with ulcerative colitis (UC)[1,2]. They appear mostly during the course of the disease, very rarely being described at the disease onset[1]. Giant inflammatory polyp - GIP (> 1.5 cm in length or diameter) is exceptionally rare[3]. Only three adult cases with GIP at the onset of the UC have been described, these all being localized forms[4-6]. To the best of our knowledge, no pediatric case with diffuse GIP as a presenting feature of the UC has been previously described. We report a case of a male teenager, who presented with abdominal pain, bloody diarrhea, palpable abdominal mass, protein-losing enteropathy and anemia and was diagnosed with diffuse GIP and moderate-to-severe ulcerative pancolitis. We discuss our case with respect to the literature and highlight the current concepts in managing the treatment, given also the high risk of colorectal cancer (CRC).

Case report

A 14-year 1-month-old male, without any significant personal/family medical history, presented to our clinic in April 2006, with diffuse abdominal pain and bloody diarrhea (3-6 diurnal and nocturnal daily stools), for 16 days. He had been previously admitted into two hospitals and treated with antibiotics for presumed gastroenteritis, without any effect. In our clinic, the physical examination revealed pathologically pallor, palpebral edema, intense diffuse abdominal tenderness, palpable mass in the right lower paraombilical area (~4/8 cm), with diminished abdominal sounds in that region, and bloody loose stools at the digital rectal examination. Somatic development was within the normal range (weight 46 kg, p10-25; height 161 cm, p50; BMI 17.7 kg/m^2, p10-25).

Clinically, the following hypotheses have been considered: persistent infectious diarrhea, antibiotic-associated diarrhea, inflammatory bowel disease or diverticulitis, associated with possible tumor.

Inflammatory markers were normal (ESR, fibrinogen, CRP, no neutrophilia). Basic blood tests have shown hypochromic microcytic hyposideremic anemia (Hb 10.3 g%, VEM: 75.5 fl, HEM: 24.5 pg, Fe=9 μg/dl) and hypoalbuminemia – 1.8g% [n 3.5-4.5 mg%]; liver, pancreatic, hemostasis and urinary tests were normal. Immunologic panel (including antinuclear antibodies, antidsDNA, serum immunoglobulins, pANCA, cANCA, ASCA) was normal. HIV, cytomegalovirus Ig M and Epstein-Barr virus Ig M antibodies were negative.

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Neither pathogens nor dysbiosis were detected in the stool (including toxins against Clostridium difficile). On the next day, the patient's condition worsened, with insupportable abdominal pain. A colonoscopy was planned, but the surgeons suspected an ileo-colonic intussusception, requiring the patient to be transferred to their department. Two days later, a laparotomy was performed, however, without revealing any pathology. The patient was subsequently treated with antibiotics (Amikacin, Cefuroxime, Clindamycin), for an associated mandibular osteomyelitis and was dismissed from the surgery department 6 weeks later. In the hospital, as well as at home, he continued to present intermittent bloody diarrhea and abdominal pain. Readmitted in our clinic 2 months after the first visit, we found the same physical characteristics, except for the absence of the abdominal mass and the presence of weight loss (1 kg). Laboratory results were not much different than the first admission, except for the worsening of anemia (Hb 9.9 g %). Lower endoscopy revealed, surprisingly, hundreds of diffuse colonic polyps, sized between 0.5 and 2 cm, most of them being sessile, with various shapes. The intervening mucosa (difficult to be appreciated given the density of polyps) showed erythema, loss of vascular pattern, ulcerations, friability and petechiae (Fig. 1). All lesions (including polyps) were much less pronounced in the rectum. Terminal ileum was normal. Upper digestive endoscopy was normal. The endoscopic diagnosis considered a diffuse colonic polyposis (with rectal sparing), inflammatory and/or adenomatous, in the settings of a possible active ulcerative colitis with relative rectal sparing. The histopathology report (a few days later) showed typical features of inflammatory polyposis (Fig. 2) and chronic active diffuse colitis, without any adenomatous feature. Our final diagnosis was moderate-to-severe ulcerative pancolitis, with diffuse GIP. A treatment with Prednisone and Salofalk was administered, according to the existing guidelines.

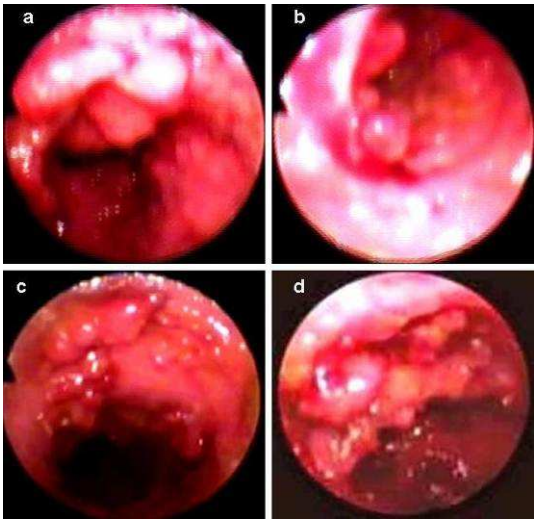

Fig. 1. Giant inflammatory polyposis coli in ulcerative colitis – colonoscopic features: multiple polyps, with various shapes, mostly sessile; the intervening mucosa (difficult to be appreciated because of the density of polyps) shows erythema, loss of vascular pattern, haemorrhage and ulcerations; a – sigmoid colon; b – transverse colon; c - descending colon; d – ascending colon.

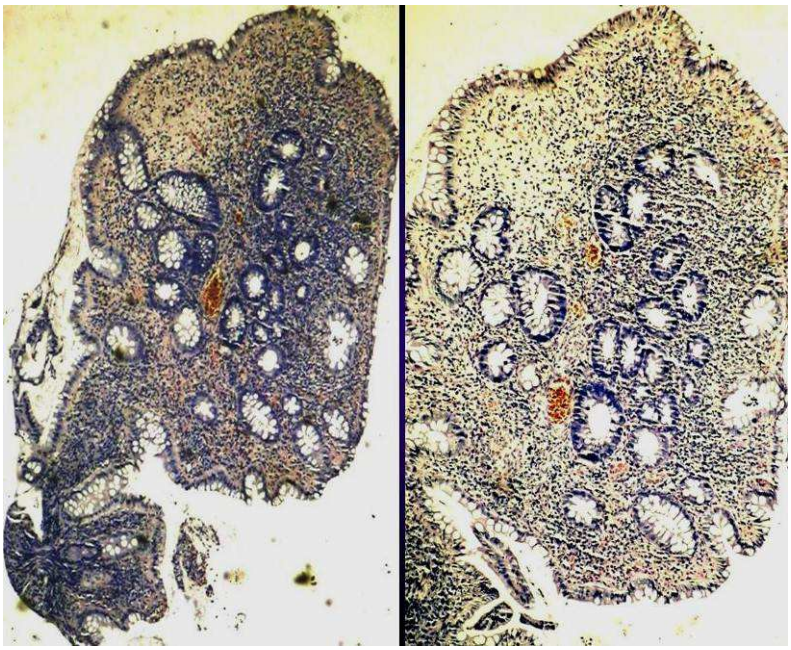

Fig. 2. Inflammatory polyps in ulcerative colitis – microscopical features: protruding lesions consisting of regenerated mucosa, with areas of granulation tissue, covered by normal epithelium, without ulcerations.

One month later, the follow-up visit showed triple clinical, endoscopic and histological remission of the UC, with marked reduction in the number and size of the polyps. After tapering the steroids, 3 months later, colonoscopy showed remission of the UC, but with microscopical activity. To prevent the clinical flare-up, we restarted the steroid therapy, adding Azathioprine, given the steroid-dependency. The patient had 18 follow-up visits in our clinic (last in April 2010), with at least 2 colonoscopies/year. He remained in histological remission for 5.6 years, with only a few diffuse scattered inflammatory polyps and a good somatic development (18 year-old male, weight 70 kg, p50-75; height 170 cm, p10-25; BMI 24.22 kg/m^2, p75-85). He did not develop any severe infection or side effects related to the therapy. Afterwards, he was transferred to an adult IBD clinic.

Discussions

Many aspects could be considered in this patient: the probable diagnosis at the first presentation - intestinal

intussusception due to GIP, with spontaneous resolution; the extreme rarity and also the severity of the diffuse GIP at the disease onset, with protein-losing enteropathy; the uselessness of the serological inflammatory markers in assessing the activity of the disease, contrasting with other reports[7]; the relative macroscopical rectal sparing (atypical in adult UC, but present in up to 30% of pediatric patients[8]); the patient's high risk of developing CRC; the crucial role of the colonoscopy in monitoring disease activity/surveillance for dysplasia and/or CRC.

Inflammatory polyps appear as intraluminal projections of inflamed or regenerated mucosa, covered by normal/ulcerated epithelium[9]. The classification of the inflammatory polyposis was made more than 30 years ago, considering the following types[10]: localized multiple polyposis (small polyps, < 5 mm with focal distribution), giant polyposis (large polyps, >1.5 cm, generally with focal distribution), generalized polyposis (small polyps with diffuse distribution) and filiform polyposis (elongated slender polyps, with diffuse or random distribution). Our case is peculiar, since he presented with a giant polyposis, but in a diffuse form, which is not included in the above classification.

An outstanding review of published cases with GIP in inflammatory bowel disease (1965-2007) found only 81 GIP in 78 patients[1], attesting the rarity of this entity. Moreover, as the authors stated, they had only 1 case in 10 years, out of 1921 patients with UC[1]. GIP has been found to be very rare both at the CU onset (no case in children and 3 in adults, these all being localized[4-6]) and during the course of the disease (4 pediatric cases, 2 with total colectomy and 2 with partial colectomy, all being localized[11-14] and less than 40 cases in adults[rev. in 1]). We believe that in our case the polyps were already expressed at the first admission, with protein-losing enteropathy and intestinal intussusception, which resolved spontaneously. This makes our case very intriguing, with respect to the very short time of developing the GIP (16 days). Even if we consider 2 months (until the colonoscopy), the period is still unusually short, most cases developing these polyps in years. That is why we considered also the possibility of another type of polyposis (e.g. adenomatous), superimposed on an active colitis. We found in the literature one case associating adenomatous polyposis coli and UC[15], so that our supposition during the colonoscopy could have been right. In the classical differential diagnosis of the GIP, adenomatous polyp is included, but the main fear is that of an adenocarcinoma. Other entities to be excluded are dysplasia-associated lesion or mass and lesions secondary to cytomegalovirus or other infections[1].

Most cases with GIP had extensive UC, but with localized polyps – especially in the descending and transverse colon[1]; there has been only one published case of pancolonic GIP in adults[16]. Our case is also unique in this respect in children, with GIP arising almost throughout the entire colon (only relative rectal sparing).

The clinical expression of GIP may appear as intestinal obstruction[1,17], intestinal intususception[2], abdominal pain[1], diarrhea[1], lower hemorrhage[1], and abdominal palpable mass[1]. Three cases presented with protein-loss enteropathy[13,16,18], as was our patient.

We consider that monitoring this patient by periodic colonoscopy with biopsies (2-3/year) was the best choice, both for detecting the microscopical activity/remission and for the surveillance for dysplasia/CRC.

Indeed, if before 2005 the aim of the therapy in UC was to induce and maintain the clinical remission[19], afterwards, the obtaining of the endoscopic mucosal healing started to be considered[20]. Moreover, many clinicians have lately included as a therapeutic goal the achievement of the microscopical mucosal healing[19]. The detection of an active microscopical inflammation has been associated with a 2-3-fold increased risk of a clinical relapse after 1 year[21]. By performing colonoscopy in clinical remission, we were able to detect this microscopical activity of the UC and start a treatment that avoided the patient to have another clinical flare-up. By maintaining the microscopical remission of the disease, we consider that the risk of CRC was diminished[19,22,23], since a significant association between the degree of histological inflammation and progression towards CRC has been reported in the literature[24,25]. Chronic inflammation increases oxidative stress, promotes repeated cycles of injury, regeneration, and repair, and accelerates the accumulation of oncogenic mutations[26]. Conversely, especially in adult data, mucosal healing has been associated with long-term remission rates, reduction of disease-related complications and of hospitalization and surgery[19], and this was true in our patient as well. Our patient was fortunate to keep the remission for such a long time, only with Salofalk and Azathioprine, with marked reduction in size and number of polyps, while most patients with GIP in IBD required colectomy (85%)[1]. It is also true that very often surgery has been performed as a security precaution, given the possibility of the confusion of a GIP with an adenocarcinoma[1].

Nowadays, surrogates of the microscopical healing could be considered the fecal inflammatory markers, like calprotectin[8,22]. According to the recent ECCO/ESPGHAN Consensus in pediatric UC, calprotectin levels >100-150 μg/g indicate mucosal inflammation, however its role in predicting clinical relapse needs to be further studied[8]. The same Consensus has stated that, in a patient in clinical remission, endoscopic evaluation is not routinely recommended, aside from cancer surveillance[8]. Investigation by inflammatory fecal parameters was not available at that time in our patient.

We highlight that, even if the colonic inflammation in our patient disappeared, he still has risk factors for developing dysplasia and CRC. Generally, in patients with UC, the relative risk of developing CRC is 5.7-fold increased compared with the general population[27]. High risk factors include[28,29]: young age at the UC onset, longstanding disease (cumulative risk of 1.6%, 8.3% and 18.4% after 10, 20 and 30 years of disease, respectively)[30], extensive colitis (relative risk 2 times higher)[27], family history of CRC (risk 2.5 times higher), inflammatory polyps (2-2.5-fold greater risk)[31,32], colonic strictures[31], association with sclerosing cholangitis (relative risk 4.8-fold higher than in UC without

sclerosing cholangitis), severe endoscopic/histologic inflammation, detection of dysplasia. Protective factors include: normal colonoscopy[24,31], therapy with 5-aminosalycilates[33] (although recently controversial[34]), therapy with Azathioprine[35] (but carrying a 4 times higher risk of developing lymphoma[36]), therapy with ursodeoxycholic acid in those with sclerosing cholangitis[28,29], smoking (reduced risk by 50%)[28,29] and prophylactic colectomy[37]. Probable decreasing risk factors are adherence to therapy and surveillance colonoscopies (especially chromoendoscopy and endoscopy with magnification)[28,29]. Given all this data, we consider that for the future, even if calprotectin is available, colonoscopic surveillance is mandatory in our patient, in an adult clinic.

In *conclusion,* we have reported an unusual case presenting with short-time bloody diarrhea and abdominal pain, who was found with a palpable abdominal mass and was considered as having intestinal intussusception. The association of ulcerative pancolitis and diffuse GIP (expressed with protein-losing enteropathy) at the onset of the disease represents, to the best of our knowledge, the first case in the pediatric literature. The patient was closely monitored by colonoscopy with biopsies and was kept in long microscopical remission. The presence of factors increasing the risk of CRC requires a close follow-up of this patient in the adult clinic.

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