A European Survey on Digestive Perianastomotic Ulcerations, a Rare Crohn-like Disorder Occurring in Children and Young Adults

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Statements:

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Abstract:

Background and aims: Digestive perianastomotic ulcerations (DPAU) resembling Crohn's disease lesions are long-term complications of intestinal resections, occurring in children and young adults. They are known to be uncommon, severe and difficult to treat.

Methods: In the absence of recommendations, we performed a large European survey among the members of the ESPGHAN working group on inflammatory bowel disease (IBD) in order to collect the experience of expert pediatric gastroenterologists on DPAU.

Results: 51 patients (29 males and 22 females) were identified from 19 centers in 8 countries. Most patients were followed after necrotizing enterocolitis (n=20) or Hirschsprung Disease (n=11). The anastomosis was performed at a median age (interquartile range) of 6 (1-23) months, and first symptoms occurred 39 (22-106) months after surgery. Anemia was the most prevalent symptom followed by diarrhea, abdominal pain, bloating and failure to thrive. Hypoalbuminemia, elevated CRP and fecal calprotectin were common. Deep ulcerations were found in 59% of patients usually proximally to the anastomosis (68%). During a median follow-up of 40 (19-67) months, treatments reported to be the most effective included exclusive enteral nutrition (31/35, 88%), redo anastomosis (18/22, 82%) and alternate antibiotic treatment (37/64, 58%).

Conclusion: Unfortunately, persistence of symptoms, failure to thrive and abnormal laboratory tests at last follow-up in most of patients show the burden of DPAU lacking optimal therapy and incomplete understanding of the pathophysiology.

Introduction.

Digestive perianastomotic ulcerations (DPAU) are long-term complications of intestinal resections. A first series of four patients was reported by Parashar et al. in 1988.[1] Then after, other cases were documented by Couper (1989)[2], Hamilton (1992)[3], Paterson (1993)[4], Sondheimer (1995)[5], Chari (2000)[6], Freeman (2014)[7], Chabrit Henrion (2014)[8], Frémond (2014)[9], Bass (2015)[10] and Fusaro (2018)[11]. In all, 70 patients have been reported. In addition, Crohn Disease (CD) -like phenotypes were reported in 66 patients with Hirschprung Disease[12]. Most of these patients (86%) exhibited a total colonic or a long segment aganglionosis with Duhamel procedure (84%).

According to the pooled literature[1-11], DPAU usually occur in children or young adults (median age at diagnosis: 10,5 years) especially in males (sex ratio= 1.71). Most patients underwent a resection of the ileocecal valve with an anastomosis between small bowel (SB) and large bowel (LB) in infancy (median age at surgery: 2 months). DPAU then occur months or years after surgery. They can be revealed by a large panel of clinical complaints including chronic anemia (45%), diarrhea (30%), abdominal pain (29%), bloating (11%) or various other symptoms like failure to thrive, chronic inflammation or hypoalbuminemia. The diagnosis is based on ileocolonoscopy and/or videocapsule endoscopy.[10] Ulcerations look like CD lesions, at least macroscopically (see below) and NOD2 mutations have been identified in some patients.[9]

DPAU are difficult to treat. Surgical resection of the ulcerations with redo anastomosis may be useful (43%) but recurrences are frequent, and its indication is usually restricted to a unique anastomotic ulceration accompanied by severe bleeding and/or resistance to medical treatments. Several drugs have been proposed to control the disease. Considering the clinical and endoscopic resemblance between DPAU and CD[9], 5ASA (34%), prednisone (20%), budesonide (16%), immunosuppressors (13%) and anti-TNF antibodies[7] (14%) have been proposed with variable success rates. Use of antibiotics (27%), probiotics (3%), cholestyramine (9%), sucralfate and others has also been reported. In general, based on the up-to-date clinical experience, no firm recommendation can be drawn.

In order to better understand the clinical response to different therapeutic options, we performed a large European survey among pediatric gastroenterologists who are members of the ESPGHAN working group on Inflammatory Bowel Disease (IBD). We identified 51 cases for which we recorded the clinical findings and responses to treatments.

Case reports.

The survey was sent out to all members of the ESPGHAN working group on IBD. Patients were identified from 19 centers in 8 countries.

For each patient, a standard form collected information on family medical history when relevant; birth events; digestive disease(s) and surgical interventions; clinical, biological, radiological, endoscopic and histological findings at diagnosis and at the end of follow-up. Finally, we recorded treatments and their efficacy. Considering the resemblance between DPAU and CD, we used the Pediatric Crohn Disease Activity Index (PCDAI) to

evaluate the response to treatments. A response was defined by a PCDAI decreased by at least 12.5 points while a remission was defined by a PCDAI lower than 10 points. Data were presented as median (1^{st}-3^{rd} quartiles). The study was approved by the French ethic committee at hospital Robert Debré (ref 2018-386) and adhered to the French ethic laws.

The cohort consisted in 29 boys and 22 girls (sex ratio 1.32) with a median age at inclusion of 13 (9-17) years. Most patients had a past history of necrotizing enterocolitis (n=20, 39%) or Hirschsprung Disease (n=11, 22%, figure 1A). As expected for a disease related to necrotizing enterocolitis, preterm birth was observed in a majority of documented cases (31/46). Birth weights were in the range of expected values. Patients with a past history of IBD were excluded.

The anastomosis had been performed at median age of 6 (1-23) months (fig 1B). An ileocecal resection had been performed in 47 (92%) patients and 24 (48%) were followed for a short bowel syndrome. The anastomoses were usually between SB and LB (SB-LB anastomoses, n=47, 92%) including 12 (24%) Duhamel procedures while SB-SB and LB-LB anastomoses were both found in 5 (10%) of cases (note that eight patients had more than one anastomosis at time of survey).

First symptoms occurred 39 (22-106) months after surgery. The diagnosis was made 7.5 (1-17) months later based on ileocolonoscopy (n=49) or videocapsule endoscopy (n=2). Symptoms at diagnostic were numerous and variable from one child to another (fig 1C). Anemia was the most prevalent followed by diarrhea, abdominal pain and bloating. Values of the main laboratory tests frequently indicated anemia, hypoalbuminemia, elevated CRP and fecal calprotectin (fig. 1D). Failure to thrive was also common (fig 1E).

Deep ulcerations were found in 59% of patients (fig 2), superficial ulcerations in 59% and stenosis in 8%. Ulcerations were most often proximally to the anastomosis (n=35, 68%) but less often distally (n=4, 8%) or on both sides of the anastomosis (n=6, 12%). Few patients exhibited ulcerations limited only on the anastomosis itself (n=6, 12%).

Median time from diagnosis to last visit was 40 (19-67) months. During this period, several options have been proposed to control the disease with an average of 3.2 therapeutic lines per patient (fig 3A). Treatment responses, judged according to PCDAI after therapy, were very different from one patient to another making difficult to elaborate recommendations. Redo anastomosis was at least partially effective in 18/22 (82%) patients. Among the other frequently effective options are exclusive enteral nutrition (31/35, 88%) and alternate antibiotic treatment (37/64, 58%). At last visit, antibiotics and cholestyramine were the most used suggesting that these two drugs could have beneficial effects (fig 3B). However, response to treatment was generally incomplete as shown by the persistence of symptoms (fig 3C) and abnormal laboratory tests (fig 3D) at last visit. As an added proof, failure to thrive worsened in comparison to the time of diagnosis (fig 3E, $p<0.005$ for weight and height, paired t-test).

Discussion:

DPAU are rare but often unrecognized long-term complications of infantile digestive surgery with anastomoses usually between SB and LB (including Duhamel procedures). They are usually discovered many years after the initial surgical procedure. They often manifest by serious conditions including anemia, various digestive symptoms, failure to thrive and loss of general well-being. We thus suggest that children with ileocecal resections for any other cause than IBD would be followed by a pediatric gastroenterologist at least once a year to detect DPAU in due course.

In respect to the published reports, DPAU are difficult to treat. Many therapeutic options have been tried, but no recommendation has been made to date. The present study was built to document the medical practices within a large consortium of expert European pediatric gastroenterologists. Indeed, our series is the largest one published to date and it includes patients from several European countries. It appears that no specific treatment can be generally recommended and diverse therapeutic options are in use. Exclusive enteral nutrition may be seen as an option in the light of common malnutrition, its good tolerance and its reported efficacy (at least in some patients). Alternate antibiotic treatment and cholestyramine are the most often applied options, but they are not always effective. Good results have been reported by some groups with surgical redo of the anastomosis, especially in case of severe bleeding and/or when the ulceration is located on the anastomosis itself. However, ulcerations are often multiple and located on a large portion of the SB proximally to the anastomosis hampering their resection. This is especially true in the case of short bowel syndrome, a situation frequently encountered in DPAU. Of note, fecal microbiota transplantation has been performed in 8 patients refractory to other treatments but only in two partial responses were observed.

The relationship between DPAU and CD has been discussed previously. Indeed, the presence of scattered ulcerations on the SB is reminiscent to CD lesions, especially in case of recurrence after ileocecal resection. The association between DPAU and NOD2 mutations (like for CD) further supported the idea that DPAU could be an “experimental CD” situation[9]. Of note, we failed to confirm this association in a subgroup of 10 patients genotyped for the three main CD-associated NOD2 mutations (data not shown). According to the anatomopathological documents available, granulomas were found in only three cases and most inflammatory lesions were not specific. Finally, the usually reported absence of response to classic CD treatments like immunosuppressors and anti-TNF antibodies but the here shown relative efficiency of exclusive enteral nutrition further question common mechanisms between CD and DPAU.

Several ideas may be raised to explain DPAU. An increased inflammatory reaction of Peyer patches located in the distal ileum may be discussed. Indeed, Peyer patches are more developed in children and young adults and they could be involved in disease mechanism. The loss of the ileocecal valve may also induce a local bacterial overgrow which could contribute to the inflammation. The efficacy of exclusive enteral nutrition and antibiotics may argue in favor of this explanation. Impaired postsurgical vascular/blood supply has also been proposed. In fact, no definitive explanation can be retained and further understanding

of the pathophysiological mechanism is warranted to guide improvement in management of this severe and difficult to treat condition.

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Figure legends:

Figure 1. Findings at diagnosis. A. Disease underlying the gut resection(s). B. Intervals (in months) between the indicated events. C. Frequencies of clinical symptoms. D. Values of major biological parameters. E. Height and weight values expressed as Z-scores.

Figure 2. Examples of deep ulcerations above ileocolonic anastomoses. A-B. Young adult with a short bowel syndrome after laparoschisis. C-D. Child with a limited resection of the ileocaecal region related to an intussusception.

Figure 3. Findings at last visit. A. Responses to various treatments proposed in the European centres. Full response was defined by a PCDAI < 10 while partial response was defined by a decreased PCDAI by at least 12.5 points. B. Therapeutic options still used at the end of follow up. C. Persistent symptoms. D. Values of the biological parameters. E. Height and weight values expressed as Z-scores. * exclusive and non exclusive.