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

Pediat GETAID Grp

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1 A European survey on digestive perianastomotic ulcerations, a rare Crohn-like disorder
2 occurring in children and young adults.

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20

21 Abstract:

22 Background and aims: Digestive perianastomotic ulcerations (DPAU) are ~~uncommon medium~~
 23 ~~or~~ long-term complications of intestinal resections resembling Crohn Disease lesions. They are
 24 uncommon but severe and difficult to treat conditions occurring in children and young adults.

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

28 Results: 51 patients (29 males and 22 females) were ~~identify~~recruited from 19 centers in 8
 29 countries. Most patients were followed after necrotizing enterocolitis (n=20) or Hirschsprung
 30 Disease (n=11). The anastomosis was performed at a median age of 6 months (1-23 months,
 31 1st and 3rd quartiles) and first symptoms occurred 39 (22-106) months after surgery. Anemia
 32 was the most prevalent symptom followed by diarrhea, abdominal pain, bloating and failure
 33 to thrive. Hypoalbuminemia, elevated CRP and fecal calprotectin were common. Deep
 34 ulcerations were found in 59% of patients usually proximally to above the anastomosis (68%).

35 Responses to treatment were very different from one patient to another. Alternate antibiotic
 36 treatment and exclusive enteral nutrition appeared as the best options for some groups.
 37 Length of follow-up?

38 Conclusion: At the date of last follow-up the persistence of symptoms, failure to thrive and
 39 abnormal laboratory tests in most of patients do not allow claiming strong treatment
 40 recommendations.

43 Introduction.

44 Digestive perianastomotic ulcerations (DPAU) are rare medium or long-term
 45 complications of intestinal resections. A first series of four patients was reported by Parashar
 46 et al. in 1988.¹ Then after, other cases were documented by Couper (1989)², Hamilton (1992)³,
 47 Paterson (1993)⁴, Sondheimer (1995)⁵, Chari (2000)⁶, Freeman (2014)⁷, Chabrit Henrion
 48 (2014)⁸, Frémond (2014)⁹, Bass (2015)¹⁰ and Fusaro (2018)¹¹. As whole, 70 patients have been
 49 reported. In addition, Crohn Disease (CD) -like phenotypes were reported in 66 patients with
 50 Hirschsprung Disease patients¹². Most of these patients (86%) exhibited a total colonic or a
 51 long segment aganglionosis with Duhamel procedure (84%).

52 According to the pooled literature¹⁻¹¹, DPAU usually occur in children or young adults
 53 (median age at diagnosis: 10,5 years) especially in males (sex ratio= 1.71). Most patients
 54 underwent a resection of the ileocecal valve with an anastomosis between small bowel (SB)
 55 and large bowel (LB) in infancy (median age at surgery: 2 months). DPAU then occur months
 56 or years after surgery. It can be revealed by a large panel of clinical complaints including
 57 chronic anemia (45%), diarrhea (30%), abdominal pain (29%), bloating (11%) or various other
 58 symptoms like failure to thrive, chronic inflammation or hypoalbuminemia. The diagnosis is
 59 based on ileocolonoscopy and/or videocapsule endoscopy.¹⁰ Ulcerations look like CD lesions,
 60 at least macroscopically (see below) and NOD2 mutations have been identified in some
 61 patients.⁹

Kommentoinut [KLK1]: term « interquartile range » is commonly used

muotoili: Korosta

Kommentoinut [KLK2]: This is unclear and needs supporting data. Also, would add the proportion of patients undergoing surgery as a treatment option

muotoili: Korosta

Kommentoinut [KLK3]: ...would say something like... »show the burden of DPAU lacking optimal therapy and incomplete understanding of the pathophysiology

62 DPAU are difficult to treat. Surgical resection of the ulcerations with redo anastomosis
 63 may be useful (43%) but recurrences are frequent, and its indication is usually restricted to an
 64 unique anastomotic ulceration accompanied by severe bleeding and/or resistance to medical
 65 treatments [\(ref\)](#). Several drugs have been proposed to control the disease. Considering the
 66 clinical and endoscopic resemblance between DPAU and CD⁹, 5ASA (34%), prednisone (20%),
 67 budesonide (16%), immunosuppressors (13%) and anti-TNF antibodies⁷ (14%) have been
 68 proposed with variable success rates. Use of antibiotics (27%), probiotics (3%), cholestyramine
 69 (9%), sucralfate and others has also been reported [\(add ref\)](#). As whole no firm
 70 recommendation can be drawn.

71 In order to better understand the clinical response to different therapeutic options, we
 72 built a large European survey among pediatric gastroenterologists, members of the ESPGHAN
 73 working group on Inflammatory Bowel Disease [\(IBD\)](#). We identified 51 cases for which we
 74 recorded the clinical findings and responses to treatments.

75

76 Case reports.

77 The survey was sent out to all members of the ESPGHAN working group on IBD. ~~Few~~
 78 ~~patients were included from other centers aware of this survey.~~ Patients were
 79 ~~identified~~ recruited from 19 centers in 8 countries. **The diagnosis was based on ileocolonoscopy**
 80 **(n=49) or videocapsule endoscopy (n=2).**

81 For each participant, a standard form was filled by their doctors. We collected
 82 information on familial medical history when relevant; birth events; digestive disease(s) and
 83 surgical interventions; clinical, biological, radiological, endoscopic and histological findings at
 84 diagnosis and at the end of follow up. Finally, we recorded treatments and their efficacy.
 85 Considering the resemblance between **PCDAU** and CD, we used the Pediatric Crohn Disease
 86 Activity Index (PCDAI) to evaluate the response to treatments. A response was defined by a
 87 PCDAI decreased by at least 12.5 points while a remission was defined by a PCDAI lower than
 88 10 points. Data were presented as median (1st-3rd quartiles). The study was approved by the
 89 French ethic committee at hospital Robert Debré (ref 2018-386) and followed to the French
 90 ethic laws. [Any comment on statistics?](#)

91 The cohort consisted in 29 boys and 22 girls (sex ratio 1.32) with a median age at
 92 inclusion of 13 (9-17) **years**. Most patients were followed for a past necrotizing enterocolitis
 93 (n=20, 39%) or Hirschsprung Disease (n=11, 22%, figure 1A). **Median age at anastomotic**
 94 **surgery and Length of follow up (median and interquartile range)?** **As expected for a disease**
 95 **related to necrotizing enterocolitis, preterm birth was observed in a majority of documented**
 96 **cases (31/46). Birth weights were in the range of expected values (data not shown).**

97 An ileocecal resection **(non-IBD cause) had been performed?** was performed in 47
 98 (92%) patients and 24 (48%) were followed for a short bowel syndrome. The anastomoses
 99 were usually between SB and LB (SB-LB anastomoses, n=47, 92%) including 12 (24%) Duhamel
 100 procedures while SB-SB and LB-LB anastomoses were both found in 5 (10%) of cases (note
 101 that eight patients had more than one anastomosis at time of survey).

muotoili: Yliviivattu

Kommentoanut [KLK4]: would omit this ; most likely they got information via ESPGHAN

muotoili: Korosta

Kommentoanut [KLK5]: This in yellow is a result from the survey and would include this in the third paragraph in which the cohort is described

muotoili: Korosta

Kommentoanut [KLK6]: previously you use the abbreviation DPAU

muotoili: Korosta

Kommentoanut [KLK7]: years of diagnosis ? 2000-2019 ? Or earlier ?

muotoili: Korosta

Kommentoanut [KLK8]: would omit this

muotoili: Korosta

102 The anastomosis was performed at median age of 6 (1-23) months (fig 1B). First
 103 symptoms occurred 39 (22-106) months after surgery. The diagnosis was made 7.5 (1-17)
 104 months later. Symptoms at diagnostic were numerous and variable from one child to another
 105 (fig 1C). Anemia was the most prevalent followed by diarrhea, abdominal pain and bloating.
 106 Values of the main laboratory tests frequently indicated anemia, hypoalbuminemia, elevated
 107 CRP and fecal calprotectin (fig. 1D). Failure to thrive was also common (fig 1E).

108 Deep ulcerations were found in 59% of patients (fig 2), superficial ulcerations in 59%
 109 and stenosis in 8%. Ulcerations were most often proximally to above the anastomosis (n=35,
 110 68%) but less often distally below (n=4, 8%) or on both sides of the anastomosis (n=6, 12%).
 111 Few patients exhibited ulcerations limited only on the anastomosis itself (n=6, 12%).

112 Granulomas in three with which type of ulcerations?

113 Many options have been proposed to control the disease with an average of 3.2
 114 therapeutic lines per patient (fig 3A). Treatment responses (judged according to PCDAI after
 115 therapy? at last visit?) were very different from one patient to another making difficult to
 116 elaborate recommendations. Among the most frequently efficient treatments are alternate
 117 antibiotic treatment and exclusive enteral nutrition. At the date of last follow-up, antibiotics
 118 and cholestyramine were the most used suggesting that these two drugs could have beneficial
 119 effects (fig 3B). However, response to treatment was generally incomplete as shown by the
 120 persistence of symptoms (fig 3C) and abnormal laboratory tests (fig 3D) at the last visit. As an
 121 added proof, failure to thrive worsened in comparison to the time of diagnosis (fig 3E, p<0.005
 122 for weight and height, paired t-test).

124 Discussion:

125 DPAU are rare but often unrecognized long-term complications of infantile digestive
 126 surgery with anastomoses usually between SB and LB (including Duhamel procedures). This
 127 survey was not designed for assessing the incidence of the disease, but we propose that 10%
 128 or less of operated children may be a relevant range order.

129 DPAU are usually discovered many years after the surgical procedure. They often
 130 manifest by serious conditions including anemia, various digestive symptoms, failure to thrive
 131 and loss of general well-being. We thus suggest that children with ileocecal resections for any
 132 other cause than BD would be followed by a pediatric gastroenterologist parallel to patients
 133 with IBD at least once a year to detect the DPAU in due course disease.

134 In the literature, DPAU are difficult to treat. Many therapeutic options have been put
 135 on the table, but no recommendation has been made to date. The present study was built to
 136 document the diverse medical practices within a large consortium of expert European
 137 pediatric gastroenterologists. Indeed, our series is the largest one published to date and it
 138 includes patients from several European countries. Unfortunately, it appears that no specific
 139 treatment can be generally recommended and diverse therapeutic options are in use.
 140 Antibiotics, exclusive enteral nutrition and cholestyramine may be seen as the most often
 141 applied/used proposed options, but they are not always regularly efficient. Good results have
 142 been reported by some groups with surgical redo of the anastomosis, especially in case of

Kommentoinut [KLK9]: would tell this before telling the causes for surgert

muotoili: Korosta

muotoili: Korosta

Kommentoinut [KLK10]: woul add in thre Fig3A the total number of patients on each drug just after the therapeutic option. e.g. Fecal transplantation n=8

muotoili: Korosta

Kommentoinut [KLK11]: I guess we cannot say anything on this. What is the time frame when the patients with DPAU were diagnosed (i.e. between which years ?)

muotoili: Korosta

143 severe bleeding and/or when the ulceration is located on the anastomosis itself. However,
 144 ulcerations are often multiple and located on a large portion of the ~~SB small bowel~~ ~~proximally~~
 145 ~~to above~~ the anastomosis ~~hampering making difficult~~ their resection. This is especially true in
 146 the case of short bowel syndrome, a situation frequently encountered in DPAU. Of note fecal
 147 microbiota transplantation has been ~~tried/performed~~ ~~proposed~~ in 8 patients refractory to any
 148 ~~other~~ treatment but only ~~in~~ two partial responses were observed.

149 The relationship between DPAU and CD has been discussed previously. Indeed, the
 150 presence of scattered ulcerations on the ~~SB small bowel~~ is reminiscent to CD lesions, especially
 151 in case of recurrence after ileocecal resection. The association between DPAU and NOD2
 152 mutations (like for CD) further supported the idea that DPAU could be an “experimental CD”
 153 situation⁹. Of note, we failed to confirm this association in a subgroup of 10 patients
 154 genotyped for the three main CD-associated NOD2 mutations (data not shown). According to
 155 the anatomopathological documents available, granulomas were found in only three cases
 156 and most inflammatory lesions were not specific. Finally, the usually reported absence of
 157 response to classic CD treatments like immunosuppressors and anti-TNF antibodies does not
 158 argue for common mechanisms between CD and DPAU.

159 Several ideas may be raised to explain DPAU. An increased inflammatory reaction of
 160 Peyer patches located in the distal ileum may be discussed. Indeed, Peyer patches are more
 161 developed in children and young adults and they could be involved in disease mechanism. The
 162 loss of the ileocecal valve may also induce a local bacterial overgrowth which could contribute
 163 to the inflammation. The efficacy of exclusive enteral nutrition and antibiotics may argue in
 164 favor of this explanation. However, no definitive explanation can be retained up to date for
 165 this rare but severe and difficult to treat disorder.

166 ~~Taken together...~~

167
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170
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Kommentout [KLK12]: would say something like this is challenging disease and further understanding of the pathophysiological mechanism is warranted to guide improvement in the management

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210 **Figure legends:**

211
 212
 213 Figure 1. Findings at diagnosis. A. Disease underlying the gut resection(s). B. Intervals (in
 214 months) between the indicated events. C. Frequencies of clinical symptoms. D. Values of
 215 major biological parameters. E. Height and weight values expressed as Z-scores.

216
 217 Figure 2. Examples of deep ulcerations above ileocolonic anastomoses. A-B. Young adult with
 218 a short bowel syndrome after laparoschisis. C-D. Child with a limited resection of the
 219 ileocaecal region related to an intussusception.

220
 221 Figure 3. Findings at last visit. A. Responses to various treatments proposed in the European
 222 centres. Full response was defined by a PCDAI < 10 while partial response was defined by a
 223 decreased PCDAI by at least 12.5 points. B. Therapeutic options still used at the end of follow

224 up. C. Persistent symptoms. D. Values of the biological parameters. E. Height and weight
225 values expressed as Z-scores. * exclusive and non exclusive.