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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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50 **Statements:**

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52 Data availability: The data underlying this article cannot be shared publicly due to the
53 privacy of individuals that participated in the study.

54

55 Conflicts of interest: the authors have no conflict of interest to declare.

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57 Authors contribution: CM and JPH: Study design, data analysis and writing up of the first
58 draft of the paper. All authors: Patient recruitment, data collection, writing the final version
59 of the paper.

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62

63 **Abstract:**

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

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

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

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

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85

86 **Introduction.**

87 Digestive perianastomotic ulcerations (DPAU) are long-term complications of
88 intestinal resections. A first series of four patients was reported by Parashar et al. in 1988.¹
89 Then after, other cases were documented by Couper (1989)², Hamilton (1992)³, Paterson
90 (1993)⁴, Sondheimer (1995)⁵, Chari (2000)⁶, Freeman (2014)⁷, Chabrit Henrion (2014)⁸,
91 Frémond (2014)⁹, Bass (2015)¹⁰ and Fusaro (2018)¹¹. In all, 70 patients have been reported.
92 In addition, Crohn Disease (CD) -like phenotypes were reported in 66 patients with
93 Hirschprung Disease¹². Most of these patients (86%) exhibited a total colonic or a long
94 segment aganglionosis with Duhamel procedure (84%).

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

105 DPAU are difficult to treat. Surgical resection of the ulcerations with redo
106 anastomosis may be useful (43%) but recurrences are frequent, and its indication is usually
107 restricted to a unique anastomotic ulceration accompanied by severe bleeding and/or
108 resistance to medical treatments. Several drugs have been proposed to control the disease.
109 Considering the clinical and endoscopic resemblance between DPAU and CD⁹, 5ASA (34%),
110 prednisone (20%), budesonide (16%), immunosuppressors (13%) and anti-TNF antibodies⁷
111 (14%) have been proposed with variable success rates. Use of antibiotics (27%), probiotics
112 (3%), cholestyramine (9%), sucralfate and others has also been reported. In general, based
113 on the up-to-date clinical experience, no firm recommendation can be drawn.

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

118

119 **Case reports.**

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

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

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

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

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

143 First symptoms occurred 39 (22-106) months after surgery. The diagnosis was made
144 7.5 (1-17) months later based on ileocolonoscopy (n=49) or videocapsule endoscopy (n=2).
145 Symptoms at diagnostic were numerous and variable from one child to another (fig 1C).
146 Anemia was the most prevalent followed by diarrhea, abdominal pain and bloating. Values
147 of the main laboratory tests frequently indicated anemia, hypoalbuminemia, elevated CRP
148 and fecal calprotectin (fig. 1D). Failure to thrive was also common (fig 1E).

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

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

165

166 **Discussion:**

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

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

190 The relationship between DPAU and CD has been discussed previously. Indeed, the
191 presence of scattered ulcerations on the SB is reminiscent to CD lesions, especially in case of
192 recurrence after ileocecal resection. The association between DPAU and NOD2 mutations
193 (like for CD) further supported the idea that DPAU could be an “experimental CD” situation⁹.
194 Of note, we failed to confirm this association in a subgroup of 10 patients genotyped for the
195 three main CD-associated NOD2 mutations (data not shown). According to the
196 anatomopathological documents available, granulomas were found in only three cases and
197 most inflammatory lesions were not specific. Finally, the usually reported absence of
198 response to classic CD treatments like immunosuppressors and anti-TNF antibodies but the
199 here shown relative efficiency of exclusive enteral nutrition further question common
200 mechanisms between CD and DPAU.

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

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

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214
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253

254 **Figure legends:**

255

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

259

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

263

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