Intraoperative Random Biopsies of Strictureplasty Sites Can Detect Early Small-Bowel Adenocarcinoma in Patients with Crohn's Disease

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CD, Crohn’s disease;

SBA, small bowel adenocarcinoma;

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Small bowel adenocarcinoma (SBA) may complicate intestinal inflammation in patients with Crohn's disease (CD).[1] In our institution, a 39-year old woman with small bowel CD died in 2007 of peritoneal carcinosis associated with a large small bowel mass, three years after the completion of 5 strictureplasties, and nine years after an initial ileocecal resection. At the time of strictureplasties, there were no other appreciable lesions outside of strictureplasty sites, and we hypothesized that the cancer which subsequently metastasised already existed at the time of stricturoplasty and was missed during visual examination of stricturoplasty sites. We then suggested to our surgical team to routinely perform one or two random biopsies at each strictureplasty site, even if no suspicious lesions were apparent after careful visual examination of widely opened strictures. The aim was to detect early neoplastic lesions, not visible by the naked eye by the surgeon. We report here the pilot results of this routine surveillance procedure. Between November 2010 and March 2019, 13 patients (9 males) underwent 14 surgical procedures (one patient underwent two procedures a year apart) including at least one strictureplasty in the Department of Digestive Surgery of Saint-Antoine hospital. After wide longitudinal opening of strictureplasty sites and close visual examination of the mucosa, and before sutured closure of the strictureplasty, one to three (according to stricture length) biopsies from the two innermost layers of the intestinal wall (mucosa and submucosa) were performed in each stricture, using electric scalpel. Strictureplasties were closed vertically as described by Heineke-Muckulicz. Biopsies were not frozen and examined extemporaneously, but fixed in formalin and secondary analysed by the pathologist.

For the purpose of this report, data collection and analysis were performed according to the rules of general data protection regulation. Patient management and data collection were made in the context of routine clinical management. In this pure observational context, there is no need in France for written patient consent. Fifty-eight strictureplasties were performed during the 14 surgical procedures in 13 patients. The median number of stricturoplasties per patient was 3 (range, 1-11). Strictureplasties were associated with intestinal resection in 10 cases, including 5 cases of ileocecal resection. Median age of patients at the time of strictureplasty was 37 years (range, 25-37 years). Median interval between diagnosis of CD and strictureplasty was 14 years (range, 2-31 years). During strictureplasty, no suspect mucosal lesion was observed on visual examination. In 12 of the 13 patients, the histological analysis of biopsies determined only the presence of normal mucosa or acute/chronic inflammatory changes in accordance with the diagnosis of CD. In the remaining patient, pathologic examination of one biopsy determined the presence of adenocarcinoma. The patient was a non-smoking 51-year old woman with CD of the small intestine that had been active for 28 years at the time of surgery. The phenotype of the disease was stricturing from the time of diagnosis. The clinical presentation was chronic intestinal obstruction syndrome, with occasional episodes of acute incomplete intestinal obstruction that did not require hospitalization. One year before surgery, the patient experience a first episode of acute intestinal obstruction that required hospitalization and medical treatment, but no emergency surgery. On this occasion, the patient agreed to undergo elective surgery. This option had been offered to her several times previously. During the first surgery, the surgeon noted the presence of three short 1 to 2 cm-long annular strictures, all located in a 50-cm ileal segment, 2.8 m distal to the duodenojejunal flexure, and 1.6 m proximal

to the ileocaecal valve. A continuous 40-cm non-stricturing inflammation of terminal ileum was also noted. The surgeon performed an ileocaecal resection and strictureplasty of the three ileal strictures. One of the two biopsies performed in the middle strictureplasty site revealed the presence of adenocarcinoma. The histological analysis of the distal ileal segment and of biopsies from the proximal and distal stricture revealed only acute/chronic inflammatory changes and multiple epithelioid granulomas, in accordance with the diagnosis of CD. A second surgery was performed three weeks after the first one. The 50-cm ileal segment including the three strictureplasty sites was removed (Figure 1), in association with lymphadenectomy. A 0.5-cm pT2N0 adenocarcinoma with surrounding high-grade dysplasia located in the middle strictureplasty site was confirmed histologically. No adjuvant therapy was indicated. Four years later, the patient is alive and free of cancer recurrence.

Compared to age and gender-matched individuals of general population, patients with ileal CD have a 17-fold risk of developing SBA.[2] The standardized incidence ratio even approaches 50 in patients with CD of the small intestine active for more than 8 years.[3] SBA typically arises in chronically inflamed and/or stricturing ileal lesions, and is diagnosed at a younger age than in general population. The impact of IBD drugs on the risk is unknown. The increasing evidence of previous or synchronous dysplastic lesions suggest that pathogenesis of SBA complicating ileal CD may follow an inflammation-dysplasia-cancer sequence,[4,5] as in the case of adenocarcinoma complicating colonic inflammation [1]. SBA usually cannot be diagnosed preoperatively from clinical symptoms and imaging features alone. In some patients, SBA is discovered intraoperatively by the surgeon who operates on the basis of a benign indication. In the remaining patients,

diagnosis of SBA is made from histological analysis of surgical specimens, often requiring a reoperation to achieve adequate oncological safety.

In patients with extensive mutifocal stricturing small bowel CD, strictureplasty is a useful surgical conservative technique aiming to treat intestinal obstruction without extensive resection.[6] In 1991, Ribeiro et al. reported three cases of SBA in patients admitted for strictureplasty [7]. The authors recommended that all strictures be widely opened and carefully examined prior to strictureplasty with biopsies of all suspicious areas. A first case of SBA arising from a strictureplasty site, seven years after the original operation, was reported by Marchetti et al in 1996.[8] Other sporadic metachronous cases of SBA, developing at stricturoplasty sites, have since been reported. By contrast, in a single cohort study of patients with small bowel CD who underwent 367 strictureplasties, no case of metachronous SBA developing at strictureplasty site was observed during a median follow-up of 2.5 years.[9] In conclusion, to date, the absolute risk of developing SBA at strictureplasty sites remains unclear.

The poor prognosis of SBA in CD is partly related to the fact that clinical and imaging phenotype of SBA and fibrostenotic CD cannot be easily distinguished, leading to a late diagnosis. For the purpose of strictureplasty in longstanding CD, the surgeon deliberately leaves in place segments that may contain dysplasia or cancer. In order to minimize this risk, visual detection and targeted biopsies of suspect areas of opened strictureplasty was recommended by Ribeiro et al. in 1991 [7]. In the 2018 consensus on surgery of the European Crohn's and Colitis Organization [10], routine biopsy with frozen section before performing a strictureplasty was not advised. This position was based on the low number of SBA at strictureplasty sites that have been reported at the time of the consensus.

In our centre, we performed as a routine procedure one to three random biopsies of strictureplasty sites, with postoperative histological examination. We were able to detect a case of early SBA that could not been identified by the naked eye. The patient was reoperated three weeks later and underwent small bowel resection and lymphadenectomy, with no recurrence up to now. We acknowledge that our experience in this pilot report is limited, with a small sample size. Larger prospective studies are needed for assessing the diagnostic yield of systematic random biopsies of strictureplasty sites (including the number of patients needed to detect one case of SBA not detectable by the naked eye), and therefore the clinical relevance of this detection procedure.

Table 1. Characteristics of patients and surgical procedures

	Age (year)*	Sex	Small bowel Crohn's disease location	Disease duration (year)*	Immuno-suppressive therapy*	Surgical procedure	Number of stricture-plasties	Pathology
1	37	F	J	20	ADA	SP	3	No neoplasia
2	62	M	J - I	31		SP	3	No neoplasia
3	51	F	I	26	AZA	ICR + SP	3	SBA
4	28	M	J - I	15		IR + SP	5	No neoplasia
5	38	F	I	9		ICR + SP	3	No neoplasia
6	40	M	D – J - I	23	IFX	JR + SP	6	No neoplasia
7	30	M	J - I	14	AZA	SP	5	No neoplasia
						JR + SP	3	No neoplasia
8	27	M	I	11		ICR + SP	4	No neoplasia
9	35	M	I	2		IR + SP	11	No neoplasia
10	27	M	D – J - I	2	AZA - IFX	IR + SP	3	No neoplasia
11	73	M	I	5		ICR + SP	3	No neoplasia
12	46	M	I	19		ICR + IR + SP	2	No neoplasia
13	25	F	I	5	AZA - IFX	IR + SP	1	No neoplasia

ADA, adalimumab; AZA, azathioprine; D, duodenum; F, female; IFX, infliximab; I, ileum; ICR, ileocecal resection; IR, ileal resection; J, jejunum; JR, jenunal resection; M, male; SBA, small bowel adenocarcinoma; SP, strictureplasty.
* at first strictureplasty

Figure legends

Fresh open ileal resection specimen in the patient who was diagnosed three weeks before with small bowel adenocarcinoma on random per-operative biopsies of strictureplasty sites. The two peripheral white arrows indicate the neoplasia-free strictureplasty sites. The central black arrow indicates the strictureplasty site containing an early small bowel adenocarcinoma that was not detected by visual examination when making the stricturoplasty, but diagnosed by random biopsy.

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