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ORIGINAL ARTICLE

Small bowel adenocarcinoma complicating Crohn's disease: a single-centre experience emphasizing the importance of screening for dysplasia

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Abstract Small bowel adenocarcinoma (SBA) complicating Crohn's disease (CD) is rare and generally found incidentally on surgical specimens. We report our experience in CD-associated SBA observed this last decade in a tertiary referral centre in order to update its incidence, clinical presentation and pathological features. All SBAs diagnosed in patients who underwent surgery for CD between 2006 and 2016 were retrospectively included. Clinico-pathological characteristics were reviewed, and follow-up was updated. SBA was diagnosed in 9 (1.7%) of 522 patients who underwent SB resection(s) after a median CD duration of 15 years [0–32]. The median age at diagnosis was 46 years. Seven (78%) patients had obstructive symptoms refractory to medical treatment. Pre-operative biopsy revealed neoplasia in five (56%) patients (dysplasia in three and SBA in two) justifying the surgery. Two (29%) of the seven patients with imaging had features suggestive of cancer. In all specimens, SBA developed in active ileitis with adjacent dysplasia. Stage I low-grade tubulo-glandular adenocarcinoma was observed in 33% of patients. Stage IV high-grade adenocarcinoma was observed in 56% of patients, and mucinous/signet ring cell differentiation predominated in 44% of patients. Molecular analysis showed no BRAF mutation, a KRAS mutation in one case and a microsatellite instability phenotype suggestive of Lynch syndrome in one case. After a median follow-up of 24 months [7–82], four (44%) patients died with advanced stage IV SBA. This surgical series confirms that CD-associated SBA is rare with an incidence of 1.7%. Adjacent dysplasia was present in all specimens and was identified before surgery in all patients who benefit from ileal biopsies. This strengthens the importance of screening all longstanding CD by endoscopy if surgery is not considered.

Keywords Small bowel adenocarcinoma · Crohn's disease · Inflammatory bowel disease · Dysplasia · Endoscopic screening · Molecular analysis

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Abbreviations

CD	Crohn's disease
SBA	Small bowel adenocarcinoma
CT	Computerized tomography
MR	Magnetic resonance
MSI	Microsatellite instability

Introduction

Small bowel Crohn's disease (CD) is associated with an increased risk of developing small bowel adenocarcinoma (SBA) [1]. Indeed, a prospective study performed with the large nationwide French cohort of patients with CD

(CESAME) assessed a 35-fold increased rate of SBA compared to the general population [2]. This severe complication remains rare, but the incidence of SBA in newly protocol-treated CD is not established. The profile of CD patients with high risk of SBA includes long disease duration, chronic penetrating phenotype and conservative management without resection, which nowadays encompass more and more patients managed with efficient medical treatments. Virtually, more than 90% of SBA is diagnosed on resection specimens at an advanced stage [3]. Early diagnosis of SBA in longstanding CD is a challenge but should be ideal for prognostic purpose. A classical inflammation-dysplasia–adenocarcinoma sequence is evocated in all inflammatory bowel disease (IBD)-related colorectal cancer. Detection of dysplasia by systematic biopsy is clearly the best and reliable marker of an increased risk of colonic cancer in patients with ulcerative or CD colitis [4]. The question of an efficient endoscopic screening in high-risk small bowel CD is still debatable for two reasons: first, SBA-associated dysplasia is classic but has been inconstantly found in surgical specimens (49% of patients) [5]; second, according to a recent study, a prospective endoscopic screening for neoplasia in small bowel CD had a low sensibility (33%) [6].

The aims of our study were (i) to update the incidence and prognosis of SBA in a large cohort of patients surgically treated for small bowel CD at a single expert centre and (ii) to describe the clinical presentation and the histopathological characteristics of patients with CD-related SBA.

Methods

Patients and data collection

A retrospective review using a pathological database was conducted in Beaujon Hospital from 2006 to 2016: all consecutive adult patients with small bowel resection for Crohn's disease (CD) who presented with a CD-associated small bowel adenocarcinoma (SBA) on the surgical specimen were studied. All subjects gave written informed consent.

For each patient, the following clinical data were collected from the patients' medical notes using a predefined standardized questionnaire. The following information was retrieved: age at SBA diagnosis, sex, duration of CD, location and extent of the CD, digestive symptoms at the time of SBA diagnosis, pre-operative biopsy if available done the last 3 months before surgery, type of surgery performed and survival.

When available, pre-operative images including computerized tomography (CT) scan and/or magnetic resonance (MR) imaging were retrospectively reviewed by a radiologist specialized in gastro-intestinal imaging, in order to detect stenosis with upstream dilation and/or features suggestive of neoplasia.

Pathological study

Ileal surgical specimens of CD-associated SBA were reviewed to precise grossly the presence of active lesions of CD and/or ileal stenosis, the macroscopic appearance of SBA and its location. All the slides were then independently reviewed by two gastro-intestinal pathologists. The following tumour characteristics were analysed: tumour size, predominant histological type (defined as the component representing more than 50% of the tumour, i.e. tubulo-glandular, intestinal, mucinous, signet-ring cell), degree of differentiation (low grade or high grade according to WHO Digestive Neoplasms Classification 2010 [7]) and tumour stage (according to the pTNM and the American Joint Committee on Cancer criteria). We also evaluated the presence and characteristics of associated dysplasia (raised or flat when it was macroscopically visible, low or high grade based on the Vienna classification and type based on the WHO Digestive Neoplasms Classification 2010 [7]). The distribution of the dysplastic foci was also assessed, in relation to the adenocarcinoma (adjacent versus at distance from the tumour): dysplasia was considered as adjacent to a tumour when detected on the same histological slide. In all other instances, dysplasia was considered to be at distance from carcinoma. The term neoplasia refers to intra-epithelial neoplasia (or dysplasia) and invasive adenocarcinoma.

Molecular analysis

DNA was extracted from paraffin-embedded tissues for KRAS exons 2, 3 and 4 and BRAF (exons 11 and 15) mutational status analysis. Several techniques were combined to identify gene mutations with high specificity and sensitivity. There was high-resolution melting for each exon, followed by direct sequencing of the high-resolution melting PCR product.

Microsatellite instability (MSI) analysis was performed with five consensus panel markers (BAT25, BAT26, NR21, NR22, NR24) according to the published method [8]. The GeneMapper v4.0 software allows the analysis of MSI marker migration. A MSI-positive phenotype was considered to be present if at least three markers displayed instability. Additionally, immunostainings of deparaffinized 4-mm sections were carried out with antibodies targeting hMLH1 (dilution 1/50; clone ES05; Dako), hMSH2 (dilution 1/50; clone FE11), hMSH6 (dilution 1/50; clone 44; Diagnostic BioSystems) and PMS2 (dilution 1/50; clone EP51), using the VENTANA autostainer. A nuclear staining was considered as positive, whatever the percentage of positive tumour cells.

Follow-up

Patients were followed until death or last date of follow-up. All patients were followed up after surgery clinically and with CT scan and blood markers (CEA and CA 19–9) every

3 months during the first 2 years and then every 6 months during three additional years. Furthermore, colonoscopy was performed 8–12 months after surgery.

Results

Patients' clinical characteristics

The patients' flowchart is shown in Fig. 1. Between 2006 and 2016, 9 (1.7%) of 522 patients who underwent small bowel resection for ileal CD in Beaujon Hospital had associated SBA. Pre-operative biopsies were done in 5/9 (56%) patients and were all informative, leading to a prompt surgery for CD-associated neoplasia (diagnosis of SBA in 2 patients, high-grade or low-grade dysplasia in 3 patients). In patients 3 and 8, neoplasia was diagnosed by pre-operative biopsies concomitantly with a first diagnosis of CD. In patients 5 and 7, ileal neoplasia was fortuitously found on multiple random biopsies (six to ten samples per patient) systematically done because of long-term CD, each of them with normal biopsy 5 and 6 years before, respectively. Patient 6 has been screened yearly by systematic ileal biopsies because of a previous diagnosis of CD-associated SBA done 4 years before; the histological control done the year before was normal.

SBA was incidentally found on the surgical specimen in the four remaining patients without pre-operative biopsy who underwent ileal resection for symptomatic CD stenosis refractory to medical treatment.

Clinical features of the nine patients with CD-associated SBA are summarized in Table 1. Most of the patients were males (66%) presenting in most (8/9, 89%) an isolated small bowel CD. Only one patient had an ileo-colonic CD. The median duration of ileal CD before surgery was 15 years (range 0–32 years). The diagnosis of SBA was made at a median age of 46 years (range 37–67 years). Most of the patients were symptomatic (8/9, 89%), with symptoms of small bowel obstruction in seven (77%) patients (nausea, vomiting and/or abdominal pain) and haemorrhagic stools in one patient (patient 3). Only one patient was asymptomatic (patient 7), and SBA was fortuitously diagnosed on ileal biopsies systematically done because of a high-risk CD of 15-year-old duration.

Most of the patients (8/9, 89%) underwent surgery for CD (ileo-caecal resection) for the first time. Only one patient underwent surgery for the third time (iterative ileal resection), after two resections (16 and 4 years ago) with a previous diagnosis of CD-associated SBA done 4 years before (classified pT3N0M0, R0). He presented with tumour recurrence on the ileo-ileal anastomosis.

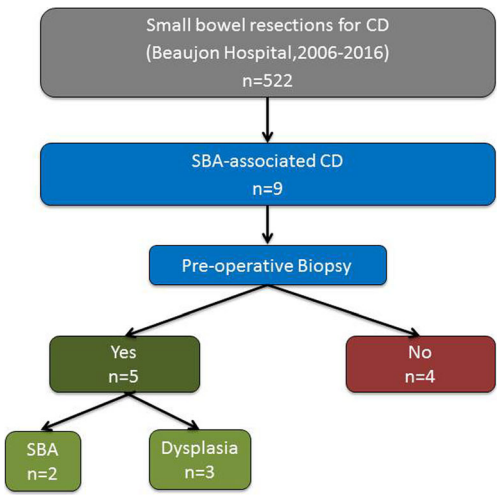

Fig. 1 Patients' flowchart. *CD* Crohn's disease, *SBA* small bowel adenocarcinoma

Imaging data

Pre-operative images were available for seven of the nine patients with CD-associated SBA. Three patients had MR imaging, two had CT scans, and two had both CT scans and MR imaging. All showed CD ileitis with marked and target enhancement of the distal ileum characteristic of active CD, complicated with stenosis with upstream dilation in three patients. Only two of the seven patients (29%) had imaging features suggestive of advanced cancer, characterized by ileal masses with regional abnormal lymph nodes and/or peritoneal nodulation suggestive of peritoneal carcinomatosis.

Surgical specimens and pathological characteristics

Pathological features of the nine patients with CD-associated SBA are summarized in Table 2 and illustrated in Figs. 2 and 3.

The median length of resected ileum was 32 cm (range 24–85 cm). All SBAs were located to the distal ileum and were all associated with active CD ileitis lesions, with stenosis in eight patients. Grossly, seven (78%) of the nine surgical specimens exhibited an obvious tumour aspect characterized by endoluminal polyps in two or by a suspicious stenosis in five specimens (Fig. 2a–c). SBA was incidentally found on microscopic examination in two patients after serial samplings of the stenosis (Fig. 2d).

On microscopic examination, all SBAs were characterized by extensive spreading: median tumour size was 5 cm (range 3–15 cm). Six (67%) SBAs exhibited high-grade differentiation, all associated with peritoneal invasion (pT4). Mucinous or signet-ring cell component predominated in four of the six high-grade SBA (44% of all SBAs) (Fig. 3a). Three (33%) SBA corresponded to low-grade tubulo-glandular adenocarcinomas with limited parietal extension (pT1/2, stage I): 2 of them were exophytic and grossly visible; the third one was flat and invisible at gross examination even after attentive re-examination.

Table 1 Clinical characteristics of the nine patients with CD-associated SBA

Pt	Age (years)	Sex	CD duration (years)	CD location	Digestive symptoms	Stenosis with dilation on imaging	Radiological features of neoplasia	Pre-operative ileal biopsy	Type of surgery (ileal length, cm)	Follow-up (months)
1	45	F	9	Ileum	Occlusion	NA	NA	NP	ICR (31)	20, DOD
2	53	M	5	Ileum	Occlusion	NA	NA	NP	ICR (32)	22, DOD
3	40	F	0	Ileum	Haemorrhage	No	No	HGD	ICR (28)	82
4	46	M	15	Ileum	Occlusion	Yes	No	NP	ICR (30)	11, DOD
5	64	M	32	Ileum	Occlusion	No	No	LGD	ICR (85)	66
6	37	M	27	Ileum	Occlusion	Yes	Yes	SBA	IIAR (12)	16, DOD
7	58	F	15	Ileum	Asymptomatic	No	No	SBA	ICR (58)	48
8	67	M	0	Ileum	Occlusion	Yes	Yes	LGD	ICR (56)	24
9	46	M	18	Ileo-colonic	Occlusion	No	No	NP	ICR (24)	26

Pt patient, *CD* Crohn's disease, *SBA* small bowel adenocarcinoma, *LGD /HGD* low/high-grade dysplasia, *SBA* small bowel adenocarcinoma, *DOD* dead of disease, *ICR* ileo-caecal resection, *IIAR* ileo-ileal anastomosis resection, *NA* not available, *NP* not performed

In total, five (56%) patients were diagnosed with SBA at an advanced stage with peritoneal and lymph node metastasis (stage IV) and the remaining four patients at an early stage without lymph node extension (stages I or II).

Associated mucosal flat dysplasia was found adjacent to SBA in all specimens and also found at distance from SBA in five (55%) of the nine specimens. According to the WHO 2010 Classification [7], dysplasia was classified high-grade "adenomatous type" in seven specimens and low-grade "villous and hypermucinous type" in two specimens, the latter being associated with mucinous or signet-ring cell invasive neoplasms.

Molecular data

KRAS and BRAF mutation status was investigated in eight patients with SBA. One tumour exhibited a KRAS mutation on exon 3 (Q61H) (patient 8). None of the tumours showed BRAF mutation. MSI status was investigated in all patients: only one tumour showed a MSI phenotype with an isolated loss of PMS2 expression (patient 5, stage II high-grade cancer in remission after a follow-up of 66 months). In this patient, the presence of HLML1 and PMS2 germline mutations, indicative of Lynch syndrome, is currently under investigation.

Follow-up

After a median follow-up of 24 months (range 11–82 months), four patients died of their cancer, all with an initial stage IV SBA with lymph node metastasis and peritoneal invasion (Table 1). No neoplastic recurrence was observed in the five remaining patients alive.

Table 2 Pathological characteristics of the nine surgical specimens with CD-associated SBA

Pt	CD activity (%)	Ileal stenosis	Gross aspect	Tumour size (cm)	Predominant tumour type	Grade of differentiation	Adjacent dysplasia	At distance dysplasia	pTNM	Stage
1	Yes	Yes	Suspicious stenosis	5	Mucinous	High	V	No	T4N2M1	IV
2	Yes	Yes	Suspicious stenosis	4	Intestinal	High	A	No	T4N2M1	IV
3	Yes	No	Polypoid lesion	15	Tubulo-glandular	Low	A	A	T1sm1N0M0	I
4	Yes	Yes	Stenosis	8	Signet-ring cell	High	V	V	T4N1M1	IV
5	Yes	Yes	Suspicious stenosis	3	Signet-ring cell	High	A	A	T4N0M0	II
6	Yes	Yes[a]	Suspicious stenosis	5	Intestinal	High	A	No	T4N1M1	IV
7	Yes	Yes	Polypoid lesion	6	Tubulo-glandular	Low	A	A	T1sm3N0M0	I
8	Yes	Yes	Suspicious stenosis	3	Mucinous	High	A	No	T4N1M1	IV
9	Yes	Yes	Stenosis	5	Tubulo-glandular	Low	A	A	T2N0M0	I

Pt patient, *CD* Crohn's disease, *V* villous and hypermucinous dysplasia, *A* adenomatous dysplasia

[a] Anastomotic stenosis

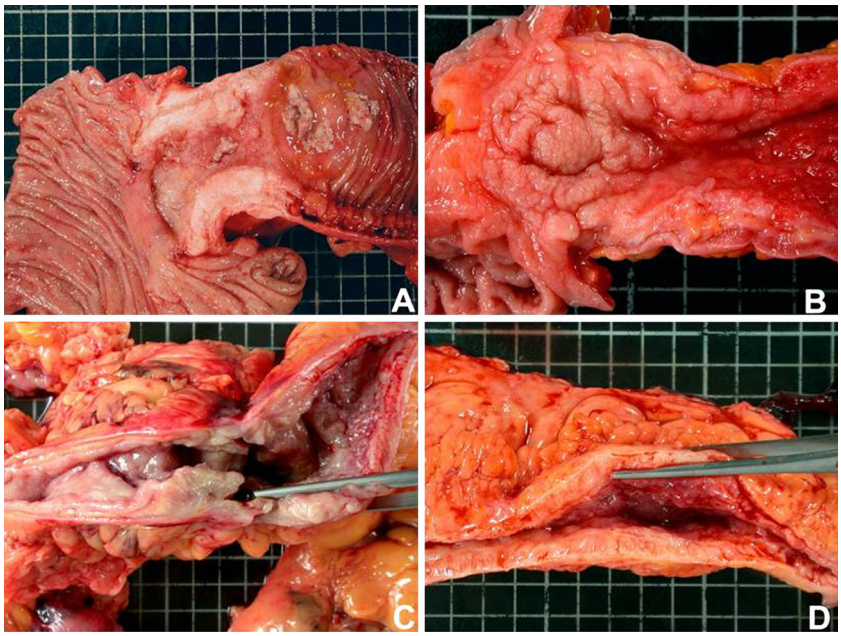

Fig. 2 Gross aspects of SBA-associated CD. **a** Patient 1, 9-year-old CD history, no pre-operative biopsy: stage IV circumferential mucinous adenocarcinoma developed on terminal ileum. **b** Patient 3, with concomitant diagnosis of CD and SBA on pre-operative biopsy: stage I polypoid low-grade adenocarcinoma. **c** Patient 5, 32-year-old history of CD with pre-operative biopsy: stage III high-grade adenocarcinoma along stenosis. **d** Patient 4, 15-year-old history of CD without pre-operative biopsy: tight and long stenosis without tumour aspect, with circumferential signet ring-cell carcinoma incidentally found on microscopic examination. *Scale square* = 1 cm

Discussion

The current study provides an updated incidence of CD-associated SBA, diagnosed between 2006 and 2016 in an expert IBD Centre. In a surgical series of 522 patients, the incidence of CD-associated SBA was 1.7%. No actual incidence of SBA in CD has been published so far [1]. SBA cumulative risks reported in 2005 were established at 0.2 and 2.2% after 10 and 25 years of small bowel CD duration, respectively [9]. Our finding is in line with previous estimations extrapolated from recent observational series [1]. It suggests that cancer occurrence in the natural history of severe small bowel CD remains a rare event.

Main clinical and prognostic characteristics of CD-associated SBA already published [1, 3] were also observed in the present study. Indeed, SBA develops only in the distal ileum, on active ileitis with stenosis, predominantly in young male (median age of 46 years) after a median CD duration of

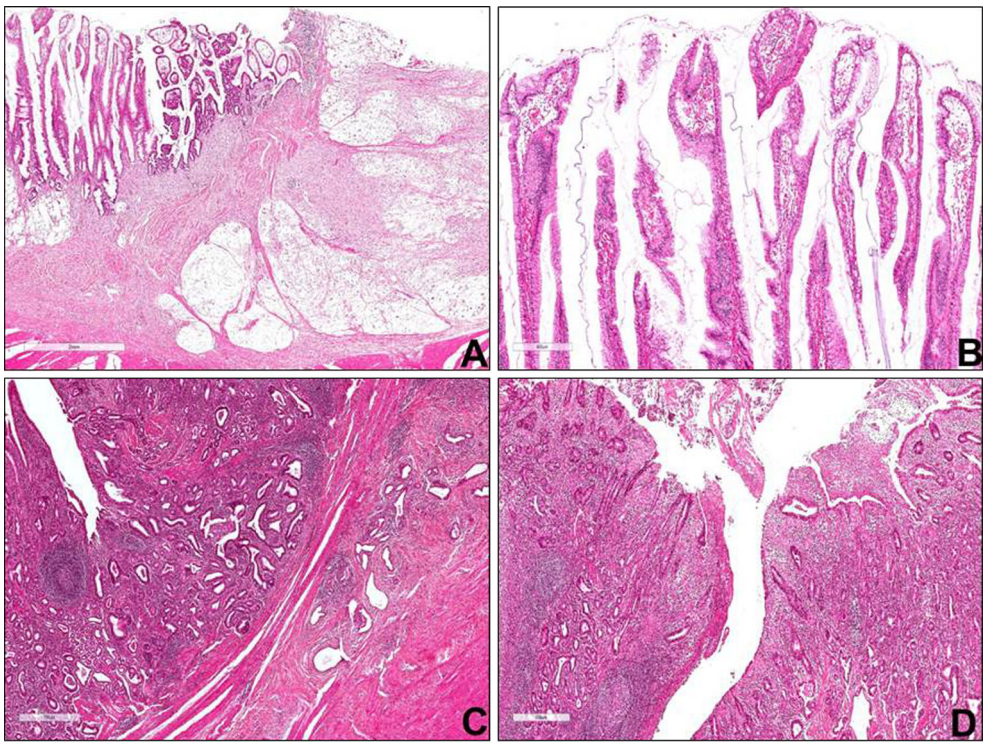

Fig. 3 Prominent histological patterns of SBA-associated CD, with adjacent dysplasia. **a**, **b** (Patient 1): high-grade SBA with mucinous differentiation invading the ileal wall (**a**), with villous and hypermucinous dysplasia present on overlying mucosae (**b**). **c**, **d** (Patient 7): low-grade tubulo-glandular adenocarcinoma made of well-differentiated glands invading superficially the sub-mucosae without stromal reaction (**c**), with low-grade tubular dysplasia present on overlying mucosae (**d**)

15 years, with no previous small bowel surgery in most cases, which is considered as a high-risk factor for SBA development. The overall poor prognosis observed in our series was related to SBA diagnosed at advanced stage with lymph node metastasis or metastatic extension in most cases, as already reported [3]. Our survival data are in line with recent results from the US registry of 179 CD-associated SBAs analysed between 1992 and 2010, reporting a 5-year overall survival of 43% [10]. The present study also confirms that imaging is not efficient to detect neoplastic lesions before an advanced stage [11].

Two peculiarities emerge from the present study. First, a preoperative diagnosis of neoplasia was done in a majority (56%) of patients thanks to an endoscopic screening, which is in contrast with the general low rate of cancer detection before surgery (less than 14% of patients in the more recent series [3]). Neoplasia was diagnosed on ileal biopsies done in 5 patients for recent aggravating symptoms or for surveillance. In our experience, ileal random biopsies done on impassable strictures were also informative in 4 patients. These findings are in conflict with a recent prospective multicentre study reporting a low sensitivity (33%) for endoscopic SBA-associated CD detection in a series of 101 patients [6]. Accordingly, the authors do not recommend systematic endoscopic surveillance of high-risk CD patients. Despite differences in terms of methodology between these two studies, our finding suggests on the contrary that endoscopy with systematic biopsies should be indicated in all CD longstanding stenosis with high risk of cancer and, if positive, followed by an adequate surgical procedure with mesenteric lymphadenectomy and free resection margins. The second peculiarity of our series was the synchronous diagnosis of CD and associated SBA observed incidentally in two patients with ileitis and dysplasia. Both were detected on random biopsies, for obstruction symptoms (in a 67-year-old male with stage IV-SBA) or for acute haemorrhage (in a 40-year-old female with stage I-SBA). These two observations highlight the possibility of SBA occurrence in never treated or newly diagnosed CD, as previously described [9].

The present study also spotlights specific pathological findings concerning cancer differentiation type specifically observed in SBA-associated CD and rarely seen in sporadic SBA: mucinous or signet-ring cell differentiation predominated in 44% of patients all diagnosed at an advanced stage and tubuloglandular differentiation in 33% of patients all diagnosed at an early stage. This latter was reported as a low-grade adenocarcinoma in 11% of IBD-related colorectal cancers [12] but was never described in CD-associated SBA series [5]. It corresponds to a very well-differentiated IBD-related neoplasm with a flat mucosal surface and no stromal reaction that mimics low-grade dysplastic glands on biopsy. Pathologists should be aware of that in small bowel CD in order to avoid underdiagnoses of these early neoplasms not detectable at endoscopy. We also searched carefully for dysplasia near or adjacent to SBA to underline the benefit of early dysplasia detection at a curable time. Indeed, all cases had dysplasia adjacent to SBA on the surgical specimens, supporting the dysplasia-carcinoma sequence of CD-associated SBA as proposed [13] and the recommendation for a prompt surgery in patients with dysplasia. Furthermore, dysplasia found at distance from the tumour in 55% of patients emphasizes the importance of surveillance after surgery to detect recurrence. In our series, "villous and hypermucinous" dysplasia was associated with aggressive mucinous or signet-ring cell cancer. This mucosal change is present in 30% of intestinal cancers developed in CD [14] and can be misdiagnosed as regenerative hyperplasia changes on ileal biopsies. Finally, no BRAF mutation was found, and KRAS mutation was found in one case which was similar to previous CD-associated SBA series and similar to alterations observed in IBD colonic or sporadic ileal cancers [5, 15].

The present study has several inherent limitations of a retrospective and monocentric analysis. Indeed, there might be an overestimation of SBA incidence compared to the general population of CD, due to a recruitment bias of an expert IBD Centre (i.e. selection of more severe patients).

In conclusion, the present study provides an estimation of CD-associated SBA incidence in an expert IBD Centre. Ileal biopsies provided diagnosis even in case of impassable stenosis. Our survival data confirm the aggressiveness of SBA diagnosed at a late stage. In light of our experience, endoscopic surveillance with systematic biopsies should be proposed in all CD patients with high-risk neoplasia criteria treated with conservative medical treatment. No consensus has been reached yet to promote such screening and the frequency of endocopic surveillance. Otherwise, a surgery discussed in a multidisciplinary staff is the optimal strategy to prevent cancer complication.

Author contributions Chloé Grolleau: data collection, data analysis, writing and literature search; Nicolas Pote: data collection, figures and English editing; Nathalie S. Guedj: data collection; M. Zappa: data collection and data interpretation; Nathalie Theou-Anton: data interpretation; Yoram Bouhnik: data interpretation; Yves Panis: data interpretation; Dominique L. Cazals-Hatem: study design, data collection, data analysis, data interpretation and writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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