Colorectal cribriform comedo-type adenocarcinoma: a distinct subtype with poor prognosis?

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Abstract

Colorectal cancer is one of the most commonly diagnosed cancers in the world. It is a heterogeneous disease with several histologic subtypes, and some of them are associated with adverse prognostic factors. Cribriform comedo-type adenocarcinoma (CCA) has been included as a colorectal adenocarcinoma subtype in the last World Health Organization (WHO) classification of gastrointestinal system tumors. Some authors have linked this subtype to an adverse prognosis, but to the best of our knowledge there is only one previous report assessing its histologic and prognostic features. We herein review a series of CCA of the colon, emphasizing its clinical and morphological features. (Acta gastroenterol. belg., **2019**, 82, **329-332**).

Key words : cribriform, carcinoma, colon, rectum, gastrointestinal.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females (1). In contrast to incidence trends, decreasing colorectal cancer mortality rates have been observed in a large number of countries and are most likely attributed to colorectal cancer screening, reduced prevalence of risk factors and/or improved treatments (2,3).

Colorectal carcinoma develops due to genetic and epigenetic alterations associated with risk, prognosis and treatment outcomes. There is a considerable stage-independent variability in patient and treatment outcomes that could be caused by molecular heterogeneity (4,5). Furthermore, molecular features seem to correlate to histologic findings. Both molecular background and tumor-microenvironment interactions are closely associated with tumor type, and this phenotypic determination has been shown to be very relevant for prognosis. Several subtypes have been recognized due to the differences in their phenotypes compared to conventional adenocarcinoma. Cribriform comedo-type adenocarcinoma (CCA) has been included as a colorectal adenocarcinoma subtype in the last World Health Organization (WHO) classification of gastrointestinal system tumors. It resembles, in architecture and cytology, a cribriform adenocarcinoma of the salivary glands or the breast; it has also been described in gallbladder, pancreas or stomach (6-8).

As far as we know, only one study has assessed the histologic features and analyzed its possible prognostic implications in colon and rectum (4).

We herein review our series of colorectal CCA, emphasizing its clinical and morphological features.

Case series

We have retrospectively reviewed the colorectal carcinoma cases diagnosed in the last decade in Hospital Clínico San Carlos, Madrid (Spain). We have retrieved 149 cases of colorectal carcinoma, 8 of which have corresponded to CCA (5.3%). We have reviewed clinical, morphological features and microsatellite instability status of these cases (Tables 1-2).

The age of our patients ranged from 60 to 82 years (mean: 74.4 years). There were 5 males and 3 females, all Caucasian. Two of them presented with rectal bleeding, two had symptoms of anemia and two complained of abdominal pain. In one of them the malignancy was an incidental finding in a PET-TC scan due to persistent fever. We have not been able to collect the clinical presentation data of one patient. None of them had neoadjuvant therapy before surgery. 4 patients had synchronous colonic adenomatous polyps of the usual tubular type with low-grade dysplasia (TALGD) and in two cases there were also hyperplastic polyps.

5 of the lesions were located in the sigmoid colon, one in the rectum, one in cecum and one in transverse colon. They measured between 2.7 and 4.8 cm (mean, 3.56 cm). Three of them were sessile polypoid lesions, three were stenosing and two presented ulceration and/or an inflammatory plastron. Diagnosis was only made when at least 90% of the tumor showed cribriform features. Two cases (cases 1 and 3) were entirely composed of cribriform glands. Percentage of cribriform pattern ranged between 90 and 100% (mean: 95.4%). Cribriform areas were always associated with necrosis. Some tumor nests were mainly solid with rounded lumens filled with necrotic material, other nests showed large cystic lumens with amorphous eosinophilic material and nuclear karyorrhexis (Figure 1). In two cases (cases 4 and 5), necrotic debris were associated with irregular

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Table 1. — **Clinical features of colorectal cribriform comedo-type adenocarcinomas**

Case	Age (years)	Sex	Race	Symptoms	Other findings
1	82	Male	Caucasian	Anemia	AD: TAHGD 15cm from anus
2	82	Female	Caucasian	Astenia and anorexia. Abdominal pain, perforation peritonitis	
3	69	Male	Caucasian	NS	AD: Submucosal lipoma in sigmoid colon
4	75	Female	Caucasian	Anemia Left iliac fossa mass	PD: Surgery due to adhesive intestinal obstruction (prior hysterectomy)
5	60	Male	Caucasian	Constitutional symptoms, left iliac fossa pain	AD: TALGD (endoscopic resection)
6	80	Male	Caucasian	Rectal bleeding	AD: Several hyperplastic polyps and two TAHGD in resection specimen
7	70	Male	Caucasian	Incidental finding, PET-CT scan due to long-term fever	PD: Central cord syndrome at C2-C3, due to abscesses by *S. aureus*
8	77	Female	Caucasian	Rectal bleeding	AD: TAHGD and hyperplastic polyp in resection specimen. Malignant epithelioid mesothelioma in parietal peritoneum samples

AD : At the time of the diagnosis. NS : Not specified. PD : Prior to the diagnosis. TALGD – Tubular adenoma with low grade dysplasia. TAHGD : Tubular adenoma with high grade dysplasia.

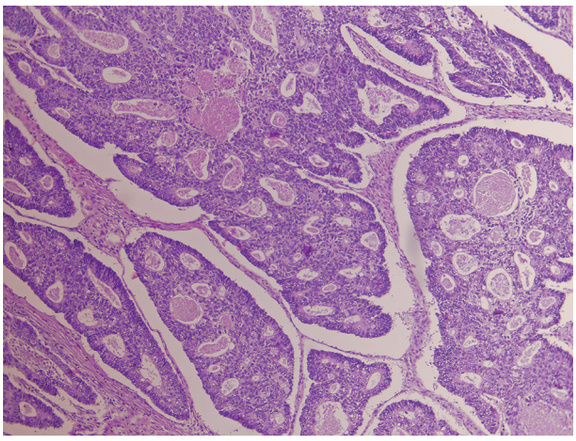

Figure 1. — Colonic cribriform comedo-type adenocarcinoma: cribriform glands with central comedo-type necrosis. (H-E, x100).

calcifications. Apart from cribriform glands with central comedo-type necrosis, tumor features were very variable. Five of them had mild intratumoral lymphocytic response (0-2 lymphocytes per high-power field), in one of them this response was marked and in the remaining two cases no tumor infiltrating lymphocytes were found. Crohn-like lymphocytic response is defined as the presence of lymphoid nodules or follicles at the tumor periphery, and it has been suggested to be associated with better prognosis. Two or more follicles must be identified in a section, and they cannot be associated with preexisting lymph nodes or mucosal invaginations. In three of our cases this response was mild, in one it was marked and in four cases no response was found. The leading front of the tumor was pushing in five cases and infiltrative in the remaining three, and tumor budding (presence of detached tumor cells or small clusters of cells at the tumor edge) was observed in three cases. 50% of cases presented desmoplastic reaction of the stroma. Tumor necrosis was seen in only one case (excluding the comedo-type necrosis in the center of the cribriform nests that allows this diagnosis).

Lymph-vascular invasion was seen in five cases, and perineural invasion in four cases (all tumors with perineural invasion had also lymph-vascular invasion). Only one case showed loss of MLH1 and PMS2 with native BRAF.

The pathologic stage of the tumors was also very variable, three were stage III, three stage II and two stage I. Lymph node metastasis were present in three cases, and none of them had distant metastases. The median number of affected lymph nodes was 3 (range : 1-7).

Follow-up period ranged between 12 and 20 months (mean: 15 months). In one of the patients (case 3), liver metastases were identified 16 months after diagnosis. He is now being treated by chemotherapy. The remaining patients are stable and being followed-up. No other metastases or early recurrences have been found.

Discussion

The WHO classification of digestive system tumors have recently recognized colorectal CCA as an adenocarcinoma conformed by polygonal cells with abundant cytoplasm growing in solid nests with foci of central necrosis. However, this entity is still poorly delineated. There is no clear-cut defining criteria as the minimum cribriform component that allows classification of an adenocarcinoma as a CCA. Besides, initial reports considered that CCA should be considered a high grade lesion, but there are few reports to confirm this allegedly bad prognosis. Some authors associate CCA with a higher incidence of lymph node metastasis and lymph-vascular invasion, and believe that this pattern is related to poor survival (1). However, in our series only half of the cases have shown metastasis or lymph vessel invasion and it remains to be shown whether CCA has a worse outcome

Table 2. — **Pathological and radiological features of colorectal cribriform comedo-type adenocarcinomas**

Case	Location / Size (cm)	Macro	Biopsy	Microscopy	Molecular	Stage (TNM)
1	Sigmoid colon (25 cm from anus) 4.8x3.4	Fibrin-covered ulcerated lesion, hard in consistency	LGA	ILR/PLR - Mild VI/PI - No AF- Pushing Budding - Yes Desmoplasia - No Necrosis – No Grade – Low 100% cribriform	Performed No MSI	pT2 pN0 M0 (I)
2	Rectum (9 cm from anus) 3x3	Increased consistency of rectal wall, related to superficial inflammatory adhesion	Not performed	ILR/PLR - Escaso VI/PI – Yes/No AF – Infiltrative Budding - No Desmoplasia - Yes Necrosis – Yes Grade – Low 93% cribriform	Performed No MSI	pT4a pN0 M0 (IIB)
3	Transverse colon (100 cm from anus) 2.8x2.5	Vegetating polypoid lesion with depressed center	LGA	ILR/PLR - Mild VI/PI - No AF - Infiltrative Budding - No Desmoplasia - Yes Necrosis – No Grade – Low 100% cribriform	Performed No MSI	pT3 pN0 M0 (IIA)
4	Sigmoid colon (20 cm from anus) 4x2	Circumferential, friable. Partial stenosis	LGA	ILR/PLR - No VI/PI – Yes/yes AF – Pushing Budding - Yes Desmoplasia - No Necrosis – No Grade – High 95% cribriform	Performed No MSI	pT3 pN2b pN0 (IIIC)
5	Sigmoid colon (45 cm from anus) 3.5x3	Concentric, obstructive and friable lesion	LGA	ILR/PLR - Mild /No VI/PI – Yes/Yes AF – Pushing Budding - No Desmoplasia - No Necrosis – No Grade – High 90% cribriform	Performed No MSI	pT4a pN1a M0 (IIIB)
6	Sigmoid colon (20-25 cm from anus) 4.2x3.6	Sessile polyp with lobulated surface	LGA	ILR/PLR – Mild / No VI/PI - No AF – Infiltrative Budding - No Desmoplasia- Yes Necrosis- No Grade – High 95% cribriform	Performed No MSI	pT4 pN0 M0 (IIB)
7	Cecum 3.5x3.4	Sessile polyp with smooth surface	LGA	ILR/PLR – Marked VI/PI – Yes/Yes AF – Pushing Budding - No Desmoplasia - Yes Necrosis- No Grade – High 93% cribriform	Performed Loss of MLH-1 and PMS-2 Native B-RAF	pT2 pN0 M0 (I)
8	Sigmoid colon (20 cm from anus) 2.7x2.7	Lesion with irregular surface affecting one quarter of the circumference	LGA	ILR/PLR - No VI/PI- Yes/Yes AF – Pushing Budding - Yes Desmoplasia - No Necrosis – No Grade – High 97% cribriform	Performed No MSI	pT3 pN1a M0 (IIIB)

LGA : Low grade adenocarcinoma. ILR : Intratumoral lymphocytic response. PLR : Peritumor lymphocytic response. VI : Lymph-vascular invasion. PI : Perineural invasion. AF : Advancing front.

compared with conventional tumors with the same pathological stage.

Cribriform pattern can be easily identified by experienced pathologists. However, the assessment of the percentage of cribriform areas can be difficult and it is subject to inter and intra-observer variability. These tumors must be distinguished from metastatic cribriform carcinoma of the salivary glands or breast. However, this event is very rare. Immunohistochemical markers such as estrogen and progesterone receptors, GDCPF-15, mammaglobin and CDX-2 can be helpful. The immunohistochemical profile is identical to primary intestinal adenocarcinoma.

Regarding their molecular features, Chirieac et al. studied p16, p14, MGMT, hMLH1, MINT1, MINT2 and MINT3187 in 87 sporadic microsatellite-stable colorectal carcinomas. They found a median cribriform area of 30% and concluded that CpG island methylation was associated with the presence of cribriform glands (p=0.02) (9).

In the Lino-Silva et al. series, this subtype accounted for 7.3% of all colonic carcinomas (4). Compared with conventional intestinal adenocarcinoma, they found increased subserosal and serosal, lymph-vascular and perineural invasion (the last two were statistically significant findings). Local recurrence rate was also higher in CCA. However, in the statistical analysis only those cases in stage III demonstrated that the survival was lower in the cribriform group. The authors suggest that the percentage of cribriform component should be estimated in all colorectal adenocarcinomas, to determine if this pattern leads to a more aggressive behavior even when present in less than 90% of the tumor.

Two recent studies have assessed the prognostic impact of cribriform carcinoma in lung and breast cancer. Warth et al. studied 28 cribriform predominant pulmonary adenocarcinomas (CPA). They compared CPAs to the five adenocarcinoma growth patterns defined by the 2015 WHO classification. CPAs showed the second highest proliferative capacity and the worst disease-free survival of all subtypes (10). However, Liu et al. studied 618 cribriform carcinomas of the breast and they had smaller size, less nodal metastasis and better disease-free survival than invasive carcinoma of no special type (11). So, cribriform carcinomas have shown unique clinicopathological features in other tumors.

Our small series of CCA is very heterogeneous. Demographic features of our patients are very similar to that of conventional adenocarcinomas (elderly patients, slight male preponderance). Histopathological features have also been varied among the cases. Our follow-up is still too short to draw conclusions, but most cases had no early recurrences even in patients with lymph node involvement. Our initial findings suggest that this might be just a morphological subtype with no prognostic differences from conventional tumors, as initially suggested. However, this morphologic pattern seems to have prognostic impact in breast and lung tumors. Larger series with longer follow-up are needed to definitely settle whether this really corresponds to a different subgroup of colonic adenocarcinoma or does not deserve a separate category as a special subtype.

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