

Clear Cell Adenocarcinoma of colorectum : A case report and review of the literature

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Abstract

Primary clear cell adenocarcinoma of the colorectum is a rare neoplasm, which differs from ordinary carcinomas of the colorectum in morphological features, but shares some traits of clear cell carcinoma of other organs. The tumor is usually composed of polygonal or oval cells with abundant granular and clear cytoplasm. The nuclei are often in hyperchromatic shapes with vesicular nucleoli.

We report the first case of clear cell adenocarcinoma of the colorectum in China and review the related published cases. The tumor was located in descending colon of a 37-year-old man, and was rich in glycogen but poor in mucin. By immunoperoxidase and histochemical staining, we clarified the clinicopathological characteristics, diagnosis and differential diagnoses, and pursued its potential pathogenesis. In our case, necrosis, high mitotic activity and lymph node metastasis may suggest a highly malignant tumor and an advanced pathological stage. Nevertheless, the patient has survived for one year with the help of operation and postoperative adjuvant chemotherapy. Regardless of the stage and differentiation, surgical therapy and proper adjuvant chemotherapy are effective means to treat the clear cell adenocarcinoma of the colorectum. (*Acta gastroenterol. belg.*, 2006, 69, 235-238).

Key words : clear cell, adenocarcinoma, neoplasm, colorectum, review.

Introduction

Clear cell carcinomas usually occur in the kidney, lower urinary tract and female genital tract, and occasionally in other sites such as the larynx, breast, pancreas, stomach, biliary system, and the colon (1-6). Yet little has been reported as to their incidence, pathogenesis, morphology, growth pattern, prognosis, histochemical or immunohistochemical profile. Herein, we report a case of clear cell adenocarcinoma of the colorectum. For diagnosis and differential diagnosis, periodic acid-Schiff (PAS) and alcian blue pH 2.5 staining were used on histochemical examination, and a panel of antibodies (table 1) were applied to analyze the immunophenotypic profile of this neoplasm by the streptavidin-biotin-peroxidase method with diaminobenzidine as a chromogen.

Case report

A 37-year-old man experienced periodical melaena, diarrhea, alternating with constipation, 4-month periodical abdominal pain in the left lower quadrant, and 3 kg weight loss. What's more, the patient underwent a

periodical fever, highest to 39°C, alleviated after using antipyretic drugs. Physical examination showed tenderness in the left lower quadrant with no palpable mass. Colonoscopic examination displayed a solid tumor mass measuring approximately 8.0 cm in maximum diameter located in the wall of the descending colon, 55 cm from the anal verge. An adenocarcinoma was found by biopsy and sections of Formalin-fixed tissue stained with haematoxylin and eosin (H&E). Preoperative investigations, liver and kidney computer tomography, urography and B-mode ultrasound scans showed no evidence of primary tumor elsewhere in the body.

A radical left hemicolectomy with end-to-end anastomosis was performed. No primary tumor was detected in the kidney, bladder, prostate or urinary tract, nor were hepatic or other metastases during operation. Interestingly, during the first postoperative three days, the patient had a lower temperature (below 35°C) and bradyarrhythmia (below 55 bpm). By intravenous injection of atropine with minipump and thermal treatment, the temperature and heart rate became regular, and stayed normal since the fourth day without treatment. After radical operation, the patient underwent six courses of combination chemotherapy (FOLFIRI regimen) with irinotecan (180 mg/m² IV, day 1), leucovorin (200 mg/m² IV, days 1 and 2) and fluorouracil (400 mg/m² IV, days 1 and 2). One year later, no evidence of recurrence of the tumor was found in the colon by repeated colonoscopy, nor metastasis in other organs by B-mode ultrasound scans.

Pathological findings

Macroscopic examination

At gross examination the external surface of the specimen was massive, grayish-white, with roughly bosselated surface. The tumor, 12 cm in maximum diameter, located at the antimesenteric border and projecting towards the lumen, was found to have invaded in to the

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Table 1. — Immunohistochemical profile and methods

Antibody	Species	Company	Dilution	Incubation time	Pre-treatment	Detection
EMA	Mouse Mab	Dako	1:50	o/n, 4°C	MW.Citrate.95°C, 10 min	SP
CEA	Mouse Pab	Dako	1:300	o/n, 4°C	None	SP
CK(P)	Mouse Pab	Santacruz	1:200	o/n, 4°C	HIER/Citrate.95°C, 10 min	SP
CK19	Mouse Mab	Santacruz	1:150	o/n, 4°C	HIER/Citrate.95°C, 10 min	SP
CD117	Mouse Mab	Dako	1:100	o/n, 4°C	HIER/Citrate.95°C, 10 min	SP
Vim	Goat Pab	R&D	1:50	o/n, 4°C	MW.Citrate.95°C, 10 min	SP
CD34	Mouse Mab	Dako	1:100	o/n, 4°C	HIER/Citrate.95°C, 10 min	SP
SMA	Rabbit Pab	Dako	1:500	o/n, 4°C	None	SP
HMB45	Mouse Mab	Santacruz	1:60	o/n, 4°C	MW.Citrate.95°C, 10 min	SP
Cg-A	Mouse Pab	Dako	1:250	o/n, 4°C	MW.Citrate.95°C, 10 min	SP
Syn	Mouse Mab	Dako	1:150	o/n, 4°C	HIER/Citrate.95°C, 10 min	SP
NSE	Rabbit Mab	Dako	1:300	o/n, 4°C	MW.Citrate.95°C, 10 min	SP

EMA = epithelial membrane antigen ; CEA = carcinoembryonic antigen ; CK (P) = cytokeratin(pan) ; CD117 = CD117/c-kit ; Vim = vimentin ; SMA = smooth muscle actin ; Cg-A = chromogranin A ; Syn = synaptophysin ; NSE = neuron specific enolase ; Mab = monoclonal antibody ; Pab = polyclonal antibody ; o/n = overnight ; HIER = heat induced epitope retrieval ; MW = microwave ; SP = streptavidin-biotin-peroxidase.

serosal surface. The incised surface, dark red and fish-like, contained much necrotic matter. Twelve lymph nodes were found, the pathological tumor stage was pT4N2(5/12)M0.

Microscopic examination

The tumor cells were arranged in an acinar or nestlike pattern, contained much necrosis, and occasionally present with spurious papillary formation. The tumor cells were separated into solid aciniform by thin fibrous septa containing abundant capillaries. The tumor was entirely composed of polygonal or oval cells, with abundant granular and clear cytoplasm containing small and apparently empty vacuoles. The nuclei were hyperchromatic and had pleomorphic shapes, with prominently vesicular nucleoli (Fig. 1). Mitotic figures and double nucleoli were observed. Five of the 12 pericolic lymph nodes obtained from the specimen contained metastatic tumor whose traits were identical with the primary tumor. Surgical margins were not involved by tumor.

Sections of tumor stained by PAS technique appeared positive and negative respectively before and after diastase digestion (Fig. 2). Alcian blue pH 2.5 showed the cytoplasmic vacuoles to be nonreactive. Immunohistochemical studies showed a focal strong positive CEA reaction (Fig. 3) and diffuse positive EMA (Fig. 4). There was no immunoreactivity to other markers listed in table 1.

Discussion

In the English literature, as far as we know, the clear cell change in colorectal adenocarcinoma was first described in 1964 by Hellstrom and Fischer, who designated the lesion as a physaliferous variant of colonic carcinoma resembling the clear cells of the chordoma tumor (7). Clear cell change generally occurs in the organs of the mullerian system. So far, only nine cases of clear cell adenocarcinoma of the colorectum have been reported (table 2). The nine cases and ours have

much in common regarding cell morphology, sex (male majority), location (in the left colon or rectum), and symptoms (similar to ordinary patterns of the large intestine). Nevertheless, there are considerable difficulties with the diagnosis and differential diagnoses, in particular for metastatic renal clear cell carcinoma, as well as malignant melanoma, clear cell gastrointestinal stromal tumor, smooth muscle sarcoma, and neuroendocrine tumors.

Metastatic renal clear cell carcinoma should be seriously considered in the differential diagnoses. Preoperative imaging and intraoperative exploration can exclude the primary renal cell carcinoma. It is further confirmed by histological and immunohistochemical studies. The reaction to CEA (8-10) and EMA combined with the absence of vimentin and CKs expression (6) may be an aid in excluding renal cell carcinoma as a primary site when faced with a metastatic clear cell carcinoma. The absence of reaction to melanogenesis-associated antigen HMB45 does not support the diagnosis of malignant clear cell melanoma. The absence of special tumor markers including CD117, CD34 and vimentin was helpful in excluding the clear cell gastrointestinal stromal tumor. The absence of immunostaining of SMA can rule out smooth muscle sarcoma. Neuroendocrine tumors must be excluded, judging by preoperative high-temperature, postoperative low-temperature, bradyarrhythmia, and morphological studies. Nonreactivity of markers such as NSE, Cg-A and Syn does not support the diagnosis for neuroendocrine tumors. A great deal of necroses in the macroscopic and microscopic examinations may be responsible for the preoperative high-temperature, whereas postoperative low-temperature and bradyarrhythmia may be related to late adjustment of the thermotaxic center of the central nervous system.

According to some case reports, the clear cell adenocarcinoma of colon showed a positive reaction for PAS but negative for alcian blue (11,12,16). In other cases it reacted to neither alcian blue nor PAS (7,8,14). While our case showed strong positivity for PAS rather than alcian blue. The positivity for PAS indicates that clear

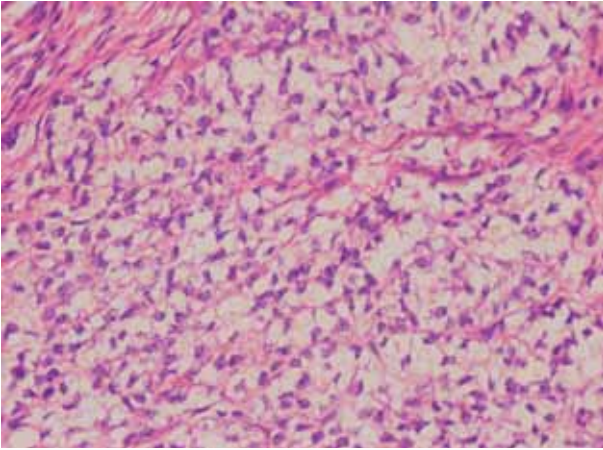


Fig. 1. — Tumor cells showed an abundant granular or clear cytoplasm and hyperchromatic nuclei with prominent nucleoli, separated into solid aciniform structures by thin fibrous septa containing abundant capillaries (H&E, original magnification, $\times 400$).

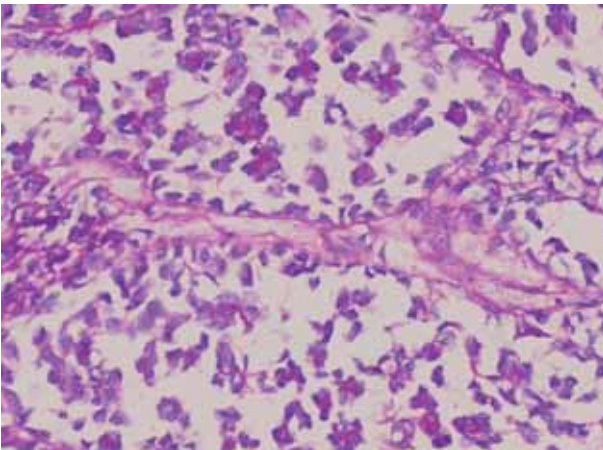


Fig. 2. — The cytoplasm of tumor cells showed diffuse PAS positive staining on histochemical examination (PAS, original magnification, $\times 400$).

cells have glycogen granules in the cytoplasm, whereas negativity for PAS might be due to the unavoidable autolysis of the specimens or to the elution of glycogen granules during processing or fixation (14,15). The mechanism for clear cell change is still ambiguous, which has been generally interpreted as an accumulation of glycogen granules (8,12,13). Electron microscopic examination confirmed the optically clear nature of the cells was due to glycogen content, but lipid could not be discerned (8). Hellstrom and Fisher supposed that the optically clear cytoplasmic spaces were primarily due to water, although some water-soluble carbohydrates might have been lost in the formalin fixative process (7). Clear cell changes can be found in both adenoma (8,15) and adenocarcinoma of the colon, and both may coexist in the same case (14), which suggests the adenoma-carcinoma sequence, valid for other histological types of col-

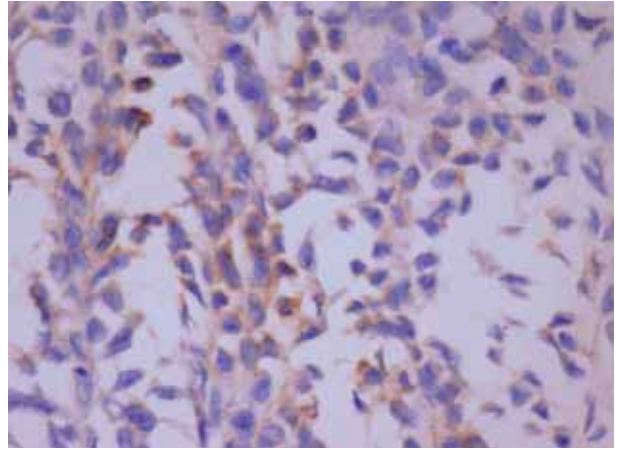


Fig. 3. — Immunoperoxidase stain for CEA was focal and strong cytoplasmic reactivity (SP, original magnification, $\times 400$).

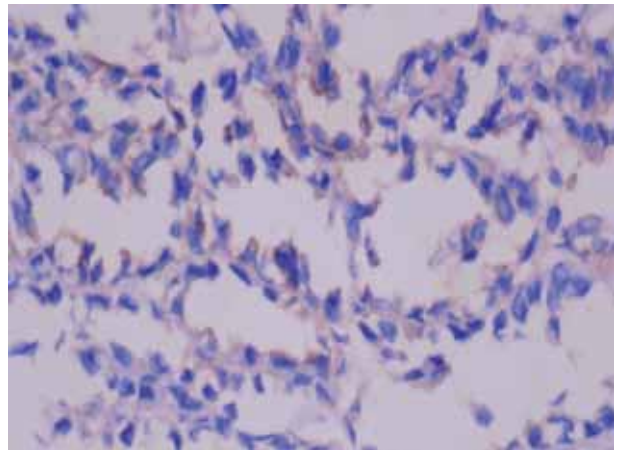


Fig. 4. — Tumor cells showed diffuse cytoplasmic or membrane immunoreactivity for EMA (SP, original magnification, $\times 400$).

orectal tumors, maybe also be valid for the clear cell adenocarcinoma of the colorectum (11,14). However, Furman speculated the clear cell changes of adenocarcinoma may not develop from adenoma but be a metaplastic process (12). McCluggage reported his case arose in endometriosis (16). Their views might represent the heterogeneous nature and varying pathogenesis of clear cell changes in the colorectum.

So few cases have been reported that the prognosis of these uncommon changes is uncertain. In our case, necrosis, high mitotic activity and lymph node metastasis may suggest a highly malignant tumor and an advanced pathological stage. The FOLFIRI regimen was used as postoperative adjuvant chemotherapy, which aims at the advanced stage and metastatic colorectal carcinomas; it is possible that the postoperative adjuvant chemotherapy and the operation contribute to the

Table 2. — Review of clear cell adenocarcinomas of the colorectum

Reference	Age (years) /sex	Location/distance from anal verge	pTNM Stage	Surgical treatment	Prognosis	Histochemical profile		Immunohistochemical profile
						PAS/PASD	AB	
Hellstrom, 1964 (7)	67/M	Rectum, 10 cm	T4N0M0	Proctectomy	alive without disease (+ 1 yr)	—/—	—	ND
Jewell, 1988 (8)	75/M	38 cm	ND	Sigmoidectomy	† (6 w)	—/—	—	CEA-, EMA-, CK(L)-, PAP-
	56/F	Sigmoid colon	ND	Sigmoidectomy	ND	ND/ND	ND	CEA-, CK(L)-, EMA-
Rubio, 1995 (11)	68/M	Splenic flexure	T3N2M0	Left hemicolectomy †	(7 mths)	—/—	—	CEA-, TPA-
Furman, 1999 (12)	ND	Rectum	ND	ND	ND	—/—	—	ND
Stenzel, 2000 (9)	ND	Rectum	ND	ND	ND	ND/ ND	ND	CEA-
McCluggage, 2001 (16)	65/F	Rectosigmoid	T4N0M1	Anterior resection	ND	—/ ND	ND	CA125-, CK7-, Collagen IV-, Laminin-, Ber-EP4-, CK20-
Braumann, 2004 (14)	89/M	Left flexure, 70 cm	T2N0M0	Segmental resection	† (20 mths)	—/—	—	CEA-, CK18-, CK20-, EMA-, CK5/6-, Vim-, Cg-A-, Syn-
Mallik, 2005 (13)	36/F	Rectum, 2 cm	T4N1M0	Sigmoidoproctectomy	ND	—/—	—	CEA-, EMA-, CA125-
Current case	37/M	Descending colon, 55 cm	T4N2M0	Left semicolon resection	alive without disease (+ 1 yr)	—/—	—	CEA-, EMA-, CK(P)-, CK19-, CD117-, Vim-, CD34-, SMA-, HMB45-, Cg-A-, Syn-, NSE-

ND = not described ; PAS = periodical acid-Schiff ; PASD = periodic acid-Schiff with diastase predigestion ; AB = alcian blue pH2.5 ; PAP = prostatic acid phosphatase ; TPA = tissue polypeptide antigen ; CA125 = cancer antigen 125 ; Ber-EP4 = a monoclonal antibody of human epithelial antigen, is directed against different tumor-associated membrane glycoproteins, which is more sensitive marker of adenocarcinomas of the ovary.

patient's survival for one year. In another case, an old man of clear cell adenocarcinoma remained well up to 20 months after a simple surgery (14). These findings suggest that surgical therapy and proper adjuvant chemotherapy are effective means to treat the clear cell adenocarcinoma of the colorectum.

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