SHORT REPORT

Colorectal small cell carcinoma in ulcerative colitis with identical rare p53 gene mutation to associated adenocarcinoma and dysplasia

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Received 12 July 2011; received in revised form 9 August 2011; accepted 11 August 2011

Abstract

Colorectal small cell carcinomas (SCCs) are rare tumors and are infrequently associated with ulcerative colitis (UC). We report a case of primary rectal SCC combined with adenocarcinoma arising in left-sided UC. Immunohistochemically, tumor cells were positive for chromogranin A, synaptophysin, and CD56 in the SCC but not in the adenocarcinoma. The patient simultaneously developed multiple lesions of adenocarcinoma and high-grade dysplasia in the sigmoid colon and rectum. To elucidate whether SCC might evolve from multipotential cells in dysplasia and/or adenocarcinoma, we examined the mutational status of TP53 and KRAS. The same clonality of these lesions including SCC was confirmed by the presence of an identical single nucleotide point mutation in TP53. KRAS mutation was not observed in these lesions. Thus, these lesions seem to have developed from the same origin. Long-standing inflammation leading to dysplasia might be responsible for the development of some SCCs in UC particularly when they are combined with dysplasia and/or adenocarcinoma.

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KEYWORDS

Small cell carcinoma; Ulcerative colitis; p53
Introduction

Primary small cell carcinoma (SCC) of the colon and rectum, either pure or mixed with another histological type, is uncommon, comprising less than 1% of colorectal cancers.1,2 Most patients present with metastatic disease at the time of diagnosis and the prognosis is particularly poor.3 Colorectal SCCs are frequently associated with an overlying adenoma or adenocarcinoma, but not associated with carcinoid tumors.4–6 According to the World Health Organization (WHO) classification, SCC is now called small cell neuroendocrine carcinoma.5

While the most common malignancy associated with ulcerative colitis (UC) is colorectal adenocarcinoma,7 SCC in a background of UC is very rare. We found only 11 cases of SCC associated with UC in the English literature and none of them have analyzed the tumors at the molecular level.8–16 It has yet to be established that long-standing UC may predispose to the development of colorectal SCC.

We present a case of simultaneous SCC and adenocarcinoma both arising in UC. By using microdissection technique, we obtained selected areas of SCC and adenocarcinoma for TP53 and KRAS mutational analysis to better elucidate the histogenesis of SCC in a background of UC.

Case report

The patient was a 36-year-old male with 17-year history of left-sided UC, which was well controlled by salazosulfapyridine. The last colonoscopy was performed 8 years ago, however he refused it since then. This time, it revealed an ulcerated mass of 3 cm in diameter and a slightly elevated mucosal lesion of 3 cm in diameter both in the rectum. Histological examination showed adenocarcinoma in both tumors. Abdominal and chest computerized tomography (CT) showed no metastasis. He underwent restorative proctocolectomy with ileal pouch anal anastomosis.

The resected specimen revealed an ulcerated mass of 4.2×4.0×1.4 cm in the rectum and widely spread irregular mucosa in the rectosigmoidal area (Fig. 1).

Histologically, high-grade dysplasia was observed in the rectosigmoidal irregular mucosa, spreading 25 cm in length from the anal verge including the ulcerated tumor and additional three adenocarcinomas.

The main tumor was composed of adenocarcinoma and SCC, which is classified as mixed adeno-neuroendocrine carcinoma in the recent WHO classification (Fig. 2). The borders of these two components were mostly clear, and SCC predominated. In the adenocarcinoma, large columnar cells formed glands variable in size. The SCC part was composed of solid sheets of small cells with hyperchromatic nuclei and scant cytoplasm (Fig. 3). Immunohistochemical staining was positive for chromogranin A, synaptophysin (Fig. 4), and CD56 in the SCC but not in the adenocarcinoma. The tumor invaded rectal adventitia with metastasis to multiple perirectal lymph nodes. Numerous lymphatics around the tumor were filled with SCC cells. The TNM stage was pT3pN2pM0.

Three additional adenocarcinomas were found in dysplastic field which were barely noticed grossly, but slightly thickened areas (Fig. 1). Two of them invaded submucosa whose TNM stages were pT1pN0pM0. The other was poorly differentiated and invaded muscularis propria, pT2pN0pM0.

To clarify the histogenesis of the SCC, TP53 and KRAS mutations were analyzed. Using microdissection technique, we obtained selected areas of SCC and adenocarcinoma components of the main tumor, satellite adenocarcinoma, dysplasia, and normal mucosa (Supplementary Fig. S1). After DNA extraction, direct nucleotide sequencing was performed. All of these 4 components harbored an identical somatic single nucleotide alteration in TP53, resulting in conversion of the codon 331 for glutamine in exon 9 to a stop codon (c.991C>T, p.Q331X) (Fig. 5). KRAS mutation of codon 12 and 13 was not observed for any of these components.

The postoperative period was uneventful. The patient was put on adjuvant chemotherapy regimen of cisplatin 60 mg/m² and irinotecan 60 mg/m². There is no evidence of recurrence 9 months after tumor resection.

Discussion

Colorectal neuroendocrine carcinoma is a rare tumor with an incidence of less than 1% of all colorectal cancers.1,2,5
Neuroendocrine carcinomas are subdivided into SCC and large cell neuroendocrine carcinoma on the basis of histopathological features and immunohistochemical findings. As is in our case, SCC consists of small, round to fusiform cells having minimal cytoplasm, fine granular chromatin, and small or absent nucleoli.5

While immunohistochemical staining for neuroendocrine markers is unnecessary to make the diagnosis of small cell carcinoma, it is often difficult to make a distinction among other tumors such as lymphomas.8–14 Including our case, most reported cases reacted positive to synaptophysin, chromogranin A, and neuron specific enolase. Neurosecretory granules were observed by electron microscopy in some cases instead of immunohistochemistry.14–16

The most common histological type of carcinoma associated with UC is adenocarcinoma.7 It has been well established that long-standing inflammation predisposes to the development of colorectal adenocarcinoma. SCC might also arise in this setting. Some authors suggested that neuroendocrine differentiation might evolve from multipotential stem cells in dysplastic epithelium, because long-standing inflammation could be responsible for the development of pancellular dysplasia.8,12,14,15 Since most of the reported cases were not surgically treated, only few reports had commented the status of surrounding mucosa.13–15 Among them, dysplasia or adenocarcinoma was found in adjacent mucosa in 3 cases13,14 while it was not found in one case.15

SCCs without a background of UC are frequently observed in association with adenoma or adenocarcinoma.4–6 Vortmeyer et al. reported that poorly differentiated neuroendocrine carcinoma and associated adenocarcinoma showed loss of heterozygosity of the same allele of APC, DCC, and TP53.6 They concluded that neuroendocrine carcinoma and associated adenocarcinoma had derived from the same cell origin. In the present study, we clearly showed that SCC and surrounding lesions possessed an identical mutation of TP53.

One of the largest TP53 mutation databases, IARC TP53 database, held by the International Agency for Research on Cancer (IARC), WHO, has collected 27,580 somatic mutations of TP53 in its latest version R15, November 2010 (http://www.iarc.fr/). In the database, the c.991C>T point mutation on exon 9, that generates a stop codon in place for the glutamine one, is quite rare, less than 0.1% of all mutations, and is not found in gastrointestinal tumors. The rareness of the TP53 mutation shown in this study strongly supports the idea that SCC seems to develop from multipotential stem cells in dysplasia or adenocarcinoma. The mutual wild type status of KRAS among the lesions further supported their identical clonality.

Greenstein et al. reported eleven cases of carcinoid associated with inflammatory bowel disease, which consisted of six cases of Crohn’s disease and five cases of UC.17 They concluded that there appears to be no evidence to substantiate a direct association between UC and histogenesis of carcinoid. The histogenesis of carcinoid and SCC in UC might be different.

Figure 3  Small cell carcinoma: solid sheet of small cells with hyperchromatic nuclei, finely granular chromatin and scant cytoplasm (HE stain).

Figure 4  Small cell carcinoma: tumor cells are positive for synaptophysin immunostain.

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Figure 5  Electropherograms of TP53 mutation analysis: All lesions showed an identical somatic single nucleotide alteration of C to T transition at the codon 331. Arrows indicate mutated nucleotide in each panel. AC, adenocarcinoma; SCC, small cell carcinoma.
Neuroendocrine carcinomas are observed in Crohn’s disease.14,18 Identical to our case, one of them was mixed adenocarcinoma and SCC of the rectum, which arose in the vicinity of high-grade dysplasia.14 The histogenesis of SCC in Crohn’s disease might be the same as in UC.

The prognosis of SCC in UC has been reported to be poor. Among the reported cases, 5 patients died within less than 15 months, and only one patient was alive for 18 months.8–12,14 In the present case, the patient underwent radical resection of the tumors and received adjuvant chemotherapy. There is no sign of recurrence for 9 months. The colorectal SCC has been reported to have sensitivity to chemotherapy akin to the pulmonary SCC.11 Thus, chemotherapy with a combination of cisplatin and irinotecan is suggested from the literature.19

In summary, we present a case of primary rectal SCC combined with adenocarcinoma arising in UC. This is a first case, which showed the identical clonality of SCC, adenocarcinoma, and dysplasia in UC. Long-standing UC may predispense to the development of not only adenocarcinoma but also SCC particularly when they are combined with dysplasia and/or adenocarcinoma.

Supplementary materials related to this article can be found online at doi:10.1016/j.crohns.2011.08.009.

Acknowledgements

There was no funding source for this study.

HH, YM, and AS designed research; SN, NO, KK and AS were the treating surgeons; HH and YS performed pathological studies; YM and AS performed genetic analysis; HH drafted the manuscript. All authors read and approved the final manuscript.

References