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Sigmoid colon carcinoma with focal neuroendocrine differentiation associated with ulcerative colitis: A case report

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ABSTRACT

INTRODUCTION: Neuroendocrine tumors of the colon and rectum are relatively rare compared to sporadic colorectal carcinoma. There are few reports of neuroendocrine tumors of the colon and rectum in patients with ulcerative colitis.
PRESENTATION OF CASE: A patient with sigmoid colon carcinoma with focal neuroendocrine features is presented. A 32-year-old man, who had been followed for ulcerative colitis for 14 years, was found to have carcinoma of the sigmoid colon on routine annual colonoscopy, and he underwent laparoscopic total colectomy. Pathologic examination showed sigmoid colon adenocarcinoma with focal neuroendocrine features.
DISCUSSION: Most colorectal carcinomas associated with inflammatory bowel disease are histologically similar to the sporadic type, and tumors with neuroendocrine features are very unusual.
CONCLUSION: Very rare case of sigmoid colon carcinoma with neuroendocrine features arising in a patient with UC was described.

1. Background

It is widely accepted that patients with ulcerative colitis have an increased risk of developing colorectal cancer. If epithelial dysplasia or carcinoma is diagnosed on surveillance colonoscopy, experts recommend elective colectomy [1]. The rates of malignant lymphoma and sarcoma have also been reported to be higher in patients with inflammatory diseases, although the etiology is not fully understood. A patient with a 14-year history of ulcerative colitis found to have sigmoid colon carcinoma with focal neuroendocrine differentiation is described. Neuroendocrine tumors (NET) in patients with UC have rarely been reported [2]. A literature review of previously reported patients is also presented.

2. Presentation of case

A 32-year-old male patient with a 14-year history of ulcerative colitis (UC), total colitis type, was followed at another hospital. The patient underwent steroid therapy for about two years, and stopped three years ago. Only 5-ASA was administered as maintenance therapy, and he was symptom-free for the last three years.

On annual colonoscopy, a slightly elevated 2-cm lesion with small central ulcer was seen in the sigmoid colon (Fig. 1). The surface of the lesion was irregular and the margin was unclear. The surrounding colonic mucosa was pale and rough, suggesting a quiescent phase of UC activity. Biopsies of the lesion showed well-differentiated tubular adenocarcinoma. Computed tomography (CT) showed partial wall thickening of the sigmoid colon with no lymphadenopathy or distant metastases. Laboratory data were normal, and tumor markers were not elevated. He was diagnosed with sigmoid colon carcinoma associated with UC, and laparoscopic-assisted total colectomy with an ileal pouch-anal anastomosis was performed. The patients' postoperative course was uneventful.

The histopathology of the specimen revealed a tubular adenocarcinoma invading to the muscularis propria (pMP) with focal neuroendocrine differentiation (Fig. 2a). Neuroendocrine features

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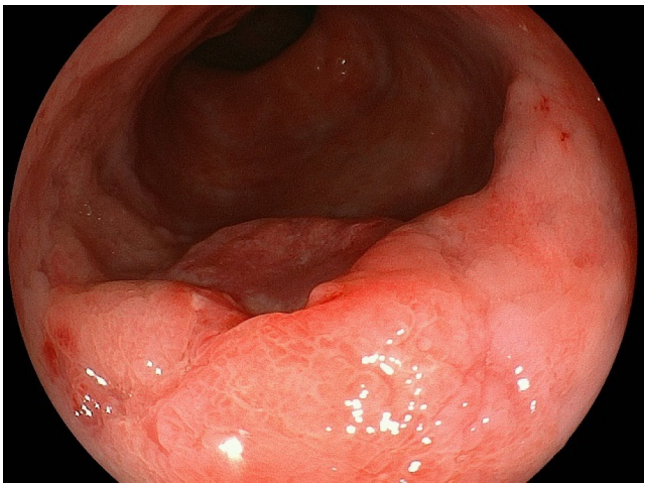

Fig. 1. Colonoscopic image of a Type 3 tumor of the sigmoid colon.

were found in the marginal area of the tumor, (Figs. 2 b, 3 a) which stained positive for both Chromogranin A (Fig. 3b) and Synaptophysin (Fig. 3c) and negative for CD56 (Fig. 3d), Ki67 index was 50%. The mucosa from the sigmoid colon to the rectum appeared to be atrophic, macroscopically. There were fibrotic changes with increased lymphoid follicles in the submucosal layer microscopically, suggesting a long history of chronic inflammation secondary to UC. The malignant tumor in the sigmoid colon was consistent with a tumor arising from chronically inflamed colonic mucosa secondary to UC. Two of 15 regional lymph nodes were found to be positive (adenocarcinoma, pN1), and the lesion was diagnosed as stage IIIa according to the general rules of Japanese classification of colorectal carcinoma [3]. Capecitabine was given as adjuvant chemotherapy for six months. At three years follow-up, there was no evidence of recurrent disease.

3. Discussion

Patients with UC are at increased risk for developing colorectal carcinoma and dysplasia. The extent of colitis and duration of the disease are the most important risk factors for the development of colorectal carcinoma [4].

However, patients with NET associated with inflammatory bowel disease have rarely been reported [2,5]. A literature search including papers published from 1980 to 2015 showed only 13 patients with NET associated with UC (Table 1). Patients in whom the carcinoid tumor was not directly associated with a dysplasia-associated lesion or mass or adenocarcinoma in UC (colitic cancer) were excluded, because carcinoid tumors can be diagnosed sporadically. Most patients had a long history of UC (median 15 years). Ten of 13 lesions were found in the recto-sigmoid, and five patients had distant metastases at the time of diagnosis. Three patients died from the disease within 15 months, although eight reports did not mention the outcome. These findings suggest a higher malignant potential of the disease compared to typical colitic carcinoma associated with UC. Risk factors are the same as colitic carcinoma including a long duration of mucosal inflammation and pan-colitis type of UC.

Dysplasia-associated lesions or masses (DALM) are elevated areas known to have an increased risk for the development of adenocarcinoma in UC. DALMs and inflammatory polyps are occasionally seen on surveillance colonoscopy in patients with UC [4,13]. A DALM does not appear like a typical adenomatous polyp, but often has a different appearance such as flat, granular, depressed and others [13]. In contrast, neuroendocrine tumors of the colon and rectum usually appear as a submucosal tumor in the early stages [14], and as type 2 or type 3 lesions in advanced stages. In this patient, the tumor showed a slightly elevated lesion with small central ulcer, and the margin was unclear. These finding were unusual for sporadic colorectal carcinoma.

Based on the 2010 World Health Organization classification, NET is stratified into two types, neuroendocrine carcinoma and mixed adeno-neuroendocrine carcinoma (MANEC), according to the proportion of neuroendocrine cells and adenocarcinoma cells. MANEC is defined as a lesion with more than 30% neuroendocrine cells. In this patient, the proportion of cells with neuroendocrine features was less than 30%, meaning a diagnosis of NET (or colorectal carcinoma with focal neuroendocrine feature), not MANEC [15].

As for NET in the gastrointestinal tract, cisplatin/etoposide is a standard chemotherapy regimen [16]. However, most NETs in the colon and rectum were MANEC in our previous study [17]. MANEC has a greater component of adenocarcinoma elements, and the efficacies of both Irinotecan/Cisplatin and 5-Ffluorouracil based chemotherapy have been reported for some patients with MANEC [17]. Adjuvant chemotherapy for patients with MANEC should also be considered because some reports indicated its effectiveness [17,18]. In the present patient, all metastatic lymph nodes appeared to be adenocarcinoma, and capesitabine was given as adjuvant therapy for six months. He has been free of recurrence for three years. It is not yet clear which chemotherapy regimen is most effective in patients with MANEC (or colorectal cancer with neuroendocrine features), because few cases have been reported.

Although colorectal carcinomas are the most frequent tumors found in patients with IBD, other types of tumors have been associated with inflammatory bowel disease, such as lymphoma and sarcoma. One hypothesis is that chronic inflammation of the colonic mucosa may cause pancellular damage involving epithelial, goblet, Paneth and neuroendocrine cells, resulting in pancellular dysplasia [5]. It has been also hypothesized that the development of neuroendocrine tumors may be secondary to distant secretion of cytokines (transforming growth factor alpha, proinflammatory cytokines, interferon gamma, tumor necrosis factor alpha, and interleukins) [19]. The combination of both inflammation –related pancellular dysplasia and secretion of systemic mediators may partially explain the development of neuroendocrine tumors in IBD patients. Serum Chromogranin A has been reported to be elevated in patients with advanced disease and those who have elevated at diagnosis. Following serum Chromogranin A levels in patients with advanced neuroendocrine tumors is recommended by the North American Neuroendocrine Tumor Society (NANETS) [20].