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Original contribution

Microcarcinoid arising in patients with long-standing ulcerative colitis: histological analysis ☆

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Summary Some case reports of neuroendocrine tumors and neuroendocrine carcinoma associated with ulcerative colitis (UC) have been published. Most neuroendocrine tumor cases are small lesions corresponding to microcarcinoids (MCs). However, published case reports have presented findings of MCs as single-case reports. Thus, the frequency of MCs is still unclear. In this study, we described the clinical and morphological features of 14 cases of UC-associated MCs and estimated the frequency of MCs. Consecutive patients with UC who underwent complete removal of the large intestine were assessed, and 135 patients were selected. Of the 135 cases, 14 cases (10.4%) in which MC lesions were observed histologically were classified as the MC group, and the remaining 121 cases were classified as the control group. Seven cases in the MC group (50%) exhibited colitic cancer. No cases in either group had distinct carcinoid tumors. All MC lesions were located in the rectum, and the sizes ranged from 0.1 to 5.5 mm. Eight cases (57%) had multiple MC lesions. The frequency of MCs in UC was estimated to be 10.4%. Most cases of MC were quite unlikely to develop into clinically distinct carcinoid tumors. Thus, when MC lesions remain microscopic, they may not represent true neoplasms, which require immediate surgical resection. Because MC often arose in cases with UC complicated by dysplasia or cancer, patients with UC whose rectal biopsies reveal MC may be at high risk of colitic cancer.

1. Introduction

Patients with chronic ulcerative colitis (UC) are known to be at risk for development of colorectal carcinoma [1]. In addition, UC-associated carcinoma (often referred to as *colitic cancer*) develops from dysplasia through a pathway called the *inflammation-dysplasia-carcinoma sequence* [2]. However, the association between neuroendocrine tumors (NETs) and UC is not clear. Only 12 case reports of UC-associated neuroendocrine carcinoma (NEC) have been published in the English literature. Although some NECs can arise from adenocarcinoma as colitic cancer, as shown in our former report [3], NETs have not been shown to develop into NEC. There have been 30 case reports of NETs and NECs associated with UC, and most NET cases were small lesions corresponding to microcarcinoids (MCs); these lesions were found to be located in the rectum and formed multiple lesions. Only 4

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articles have reported more than 1 case of carcinoid tumor: the series of Gledhill et al [4] included 2 cases, the series of Sauven et al [5] included 3 cases, the series of Greenstein et al [6] included 5 cases, and the series of Tomochika et al [7] included 2 cases. However, most case reports of MCs have been single-case reports. Thus, the frequency of MC is still uncertain.

The definition of MC has not been fully established. In previous reports, MC lesions were found to measure up to 5 mm, and no MC lesions were shown to form grossly visible masses. In this study, we first defined *MCs* as macroscopically undetectable lesions that showed a trabecular architecture or small nest structure histologically, without defining the size of the lesion. Using these criteria, we identified 14 cases of UC with MC lesions. These MC lesions measured from 0.1 to 5.5 mm in diameter on microscopic examination. Based on these findings, we reviewed the MC lesions again and compared our cases with previously reported cases.

Because MC lesions cannot be identified grossly, most reported MCs have been discovered incidentally in surgical specimens. Indeed, it is difficult to detect MC lesions before surgery, although colorectal endoscopic biopsies are often performed for surveillance of patients with UC. If a carcinoid tumor forming a mass lesion is found, endoscopic resection is a primary therapeutic approach. However, although MC is only incidentally found at biopsy in patients with UC, MC is difficult to resect endoscopically because of the difficulty in confirming the MC lesion. Considering the potential for stromal invasion of MC, endoscopic therapy may not be adequate. However, because no cases of metastatic MC lesions or MC-related death have been reported, it may not be necessary to treat MC lesions. To date, there is no consensus as to whether multiple MCs should be treated.

In this article, we evaluated the clinical and morphological features of 14 cases of UC-associated MCs. This is the first report to analyze multiple cases and estimate the frequency of MC.

2. Materials and methods

2.1. Study population

Consecutive patients with UC who underwent complete removal of the large intestine at Yokohama Municipal Citizen's Hospital between January 2011 and September 2013 were searched, and 135 patients were identified as candidates for this study. Of these patients, 20 had both the colon and rectum removed in 2 separate surgeries. The operations were performed for malignancy in 25 patients, including 24 cases of colitic cancer and 1 case of malignant lymphoma. For the rest of the patients, operations were performed because of refractory UC, steroid-dependent UC, or fulminant UC. Of the 135 cases, 14 cases (10.4%) in which MC lesions were observed histologically were classified as the MC group, and the remaining 121 cases were classified as the control group.

This study was approved by the ethics committee of Yokohama Municipal Citizen's Hospital.

2.2. Pathological evaluation and immunohistochemistry

Two pathologists assessed MC lesions (S. K. and H. H.). Resected surgical specimens were fixed in formalin, cut to a width of 5 mm, and made into paraffin blocks. At the Department of Pathology, Yokohama Municipal Citizen's Hospital, the resected large intestines from a patient with UC were histologically examined as follows: if dysplasia or cancer lesions were identified preoperatively, the entire mucosa distal from the lesion was histologically examined; if neither dysplasia nor cancer lesions were identified preoperatively, histological samples were collected along the full length of the colon with intervals of 10 cm in the mucosa. We prepared 8-139 (mean ± SD, 28.0 ± 26.6) blocks per case; the number of blocks per case in the MC group was 10-130 (56.0 ± 39.4), and that in the control group was 8-138 (25.0 ± 22.9).

Lesions that were confirmed histologically did not form macroscopic masses but did form a trabecular architecture or small nest structure, identified as MC [8]. Four-micrometer–thick sections were cut from formalin-fixed, paraffin-embedded tissues including MC lesions and were used for immunohistochemistry. Immunohistochemical staining was carried out with automated dyeing equipment (Histostainer 36A; Nichirei Biosciences, Inc, Tokyo, Japan) using Histofine Simple Stain MAX-PO(MULTI) (Nichirei Biosciences, Inc). The following immunohistochemical targets were evaluated: chromogranin A (anti–chromogranin A polyclonal antibodies; cat. no. 412 751; prediluted; Nichirei Biosciences, Inc), synaptophysin (anti-synaptophysin monoclonal antibodies; cat. no. 27G12, prediluted; Nichirei Biosciences, Inc), low–molecular weight cytokeratin (CK-LW; anti-keratin/CK-LW monoclonal antibodies; cat. no. DC10/5D3, prediluted; Nichirei Biosciences Inc), AE1/AE3 (anti-keratin/cytokeratin monoclonal antibodies; cat. no. 412 811; prediluted; Nichirei Biosciences, Inc), vimentin (anti-vimentin monoclonal antibodies; V9, prediluted; Nichirei Biosciences, Inc), neural cell adhesion molecule (anti-CD56 monoclonal antibodies; cat. no. 1B6, prediluted; Nichirei Biosciences, Inc), S-100 (anti–S-100 protein polyclonal antibodies; cat. no. 422 091; prediluted; Nichirei Biosciences, Inc), neurofilament (NF; anti-NF monoclonal antibodies; cat. no. 2F11, prediluted; Nichirei Biosciences, Inc), caudal-related homeodomain protein 2 (CDX2; anti–CDX-2 rabbit monoclonal antibodies; cat. no. EPR2764Y, prediluted; Nichirei Biosciences, Inc), Ki-67 (anti–Ki-67 rabbit monoclonal antibodies; cat. no. SP6, prediluted; Nichirei Biosciences, Inc), and neuron-specific enolase (NSE; anti-NSE polyclonal antibodies; cat. no. 422 081; prediluted; Nichirei Biosciences, Inc).

Although all 46 identified MC lesions were stained, the lesions were so small that 54% (25 lesions for chromogranin A, synaptophysin, and CK-LW) to 80% (37 lesions for CDX2) of the lesions disappeared in sequential sections and could not be fully examined immunohistochemically.

To compare the number of neuroendocrine (NE) cells in the background mucosa between the MC and control groups, using hematoxylin and eosin (H&E)–stained glass slides, NE