Ulcerative Colitis-associated Cancer/Dysplasia Detected Using Surveillance Colonoscopy Performed in the Clinical Remission Phase: A Report of Five Cases

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Abstract

We herein report five cases of ulcerative colitis-associated cancer/dysplasia. Although clinical remission had been achieved in all patients, mucosal inflammation had been resolved in only one patient. Thus, in order to prevent cancer from developing, appropriate medical therapy aiming not only to relieve the clinical symptoms, but also to suppress chronic inflammation appears to be necessary. Moreover, cancer occurred as early as 4 years after the diagnosis in one patient. In patients without complete resolution of mucosal inflammation, careful surveillance colonoscopy should be initiated in the early phase.

Key words: ulcerative colitis-associated cancer, dysplasia, clinical remission, mucosal inflammation, surveillance colonoscopy


Introduction

Patients with ulcerative colitis may develop ulcerative colitis-associated cancer/dysplasia (UCACD). The clinical risk factors for developing UCACD include the duration of disease, extent of disease, family history of colorectal cancer, concurrent presence of primary sclerosing cholangitis, onset at an early age, presence of backwash ileitis, and severity of histological inflammation (1-5). Particularly, persistent mucosal inflammation is an important risk factor for developing cancer, and it is suggested that complete resolution of mucosal inflammation may reduce the incidence of UCACD (6-8).

On the other hand, the reported significant inhibitory factors for developing cancer include prophylactic colectomy performed at the time of detecting dysplasia, regular hospital visits, endoscopic surveillance, and drug adherence (9).

Case Reports

We herein report five cases of UCACD that were detected using surveillance colonoscopy after clinical remission was achieved (Table 1, 2). Table 1 shows the overall patient characteristics, and Table 2 shows the clinicopathological features of each case.

In this article, clinical remission was defined as a Rachmilewitz clinical activity index (CAI) of 4 points or less (10).

Case 1

A 21-year-old man developed extensive, relapsing-remitting ulcerative colitis at 15 years of age. He had been treated with 5-aminosalicylic acid (5-ASA). In the early period after onset, it was difficult to maintain remission, and he was hospitalized twice for treatment. Because he was re-
Table 1. Demographic and Clinical Characteristic of Patients with Ulcerative Colitis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients n = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men/women), n (%)</td>
<td>3 (60)/2 (40)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.2 (15-67)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>11.8 (6-23)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
</tr>
<tr>
<td>Extensive colitis, n (%)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Left-side type, n (%)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Clinical course</td>
<td></td>
</tr>
<tr>
<td>Chronic-continuous, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Relapsing-remitting, n (%)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Dysplasia, n (%)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Early cancer, n (%)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Advanced cancer, n (%)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>P53 Positive, n (%)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Negative, n (%)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Family history of colorectal cancer, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Concurrent primary sclerosing cholangitis, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Presence of prolonged inflammation, n (%)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td></td>
</tr>
<tr>
<td>Present, n (%)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Absent, n (%)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

Table 2. Clinicopathological Features of Each Case.

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (y)</td>
<td>15</td>
<td>67</td>
<td>24</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Age of cancer development (y)</td>
<td>21</td>
<td>71</td>
<td>39</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td>Disease duration before cancer development (y)</td>
<td>6</td>
<td>4</td>
<td>15</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>5-ASA dose (mg/day)</td>
<td>4,000</td>
<td>3,600</td>
<td>4,000</td>
<td>4,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Duration of 5-ASA administration (y)</td>
<td>6</td>
<td>4</td>
<td>15</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Total steroid dose (mg)</td>
<td>4,284</td>
<td>8,780</td>
<td>–</td>
<td>820</td>
<td>7,375</td>
</tr>
<tr>
<td>Duration of steroid administration</td>
<td>1 year 9 months</td>
<td>2 years 5 months</td>
<td>–</td>
<td>5 months</td>
<td>3 years 9 months</td>
</tr>
<tr>
<td>Total immunomodulatory drug dose (mg)</td>
<td>88,800</td>
<td>15,000</td>
<td>–</td>
<td>46,800</td>
<td>166,500</td>
</tr>
<tr>
<td>Duration of immunomodulatory drug administration</td>
<td>5 years 2 months</td>
<td>10 months</td>
<td>–</td>
<td>4 years 4 months</td>
<td>8 years 5 months</td>
</tr>
<tr>
<td>Preoperative histological diagnosis</td>
<td>high grade dysplasia</td>
<td>well-differentiated adenocarcinoma</td>
<td>well-differentiated adenocarcinoma</td>
<td>poorly differentiated adenocarcinoma</td>
<td>high grade dysplasia</td>
</tr>
<tr>
<td>Postoperative histological diagnosis</td>
<td>well-differentiated adenocarcinoma</td>
<td>intramucosal adenocarcinoma</td>
<td>adenocarcinoma</td>
<td>signet-ring cell carcinoma</td>
<td>well-differentiated adenocarcinoma</td>
</tr>
<tr>
<td>Postoperative follow-up period (as of June 2015)</td>
<td>alive for 2 years 4 months</td>
<td>alive for 2 years</td>
<td>alive for 2 years</td>
<td>alive for 1 year 3 months</td>
<td>alive for 1 year</td>
</tr>
</tbody>
</table>

Susceptible to steroids, immunomodulatory drugs were introduced, which sufficiently improved his conditions to allow outpatient treatment. Two years later, although clinical remission (3 points on the CAI) was achieved, colonoscopy (CS) revealed active mucosal inflammation with an invisible vascular pattern, appearing red in the left side of the colon. In CS performed 3 years later, although the findings of mucosal inflammation were comparable to those of the previous CS, a protruded lesion was detected in the rectum (Fig. 1a). High-grade dysplasia was pathologically diagnosed, and surgery was performed. The surgical findings revealed a well-differentiated adenocarcinoma measuring 0.5× 0.4 cm that partially infiltrated the muscularis mucosae in the rectum. Because of the coexistence of high-grade dysplasia around the adenocarcinoma and diffuse positivity for P53 after immunostaining of the lesion (Fig. 1b, c), UCACD was diagnosed.
Case 2

A 71-year-old man developed extensive, relapsing-remitting ulcerative colitis at 67 years of age. After remission, induction therapy with prednisolone (PSL) was initiated, and clinical remission (1 point on the CAI) had been maintained by 5-ASA alone. However, CS performed 4 years later revealed exacerbated mucosal inflammation and a reddish protruded lesion in the distal sigmoid colon (Fig. 2a). Well-differentiated adenocarcinoma was pathologically diagnosed, and surgery was performed. The surgical findings revealed high-grade dysplasia/intramucosal adenocarcinoma with a major axis of 0.8 cm that was difficult to identify macroscopically in the sigmoid colon. The histopathological features of this case included the proliferative...
zone located in the middle to deep mucosal layer, a tumor existing in the ductal structure, and high-grade dysplasia existing around the tumor. Immunostaining for P53 was negative (Fig. 2b, c). It has been previously reported that even in UCACD, approximately 40% of cases are negative for immunostaining for P53 (11, 12). Therefore, UCACD was comprehensively diagnosed.

Case 3

A 39-year-old woman who developed extensive, relapsing-remitting ulcerative colitis at 24 years of age was treated with 5-ASA. Although inpatient treatment had occasionally been required, clinical remission (1 point on the CAI) was achieved when she was 31 years of age. However, CS performed 5 years later revealed active mucosal inflammation with an invisible vascular pattern, appearing red in the entire colon. Furthermore, during CS performed 3 years later, although the findings of mucosal inflammation were comparable to those obtained on the previous CS, a flat protruded lesion with a relatively well-defined margin was detected in the ascending colon (Fig. 3a). A well-differentiated adenocarcinoma was pathologically diagnosed, and surgery was performed. The surgical findings revealed an adenocarcinoma measuring 0.3 cm in the ascending colon. Because the adenocarcinoma was surrounded by low- to high-grade dysplasia and showed diffuse positivity for P53 on immunostaining (Fig. 3b, c), UCACD was diagnosed.

Case 4

A 67-year-old man had developed left-sided, relapsing-remitting ulcerative colitis at 44 years of age, which became highly active soon after onset, and chronic inflammation had persisted for many years. At 63 years of age, after remission was induced by PSL and granulocyte-monocyte adsorption apheresis, remission maintenance therapy was initiated with 5-ASA plus immunomodulatory drugs, resulting in clinical remission (1 point on the CAI). Complete resolution of mucosal inflammation was observed at 64 years of age, and the findings of CS performed 2 years later were comparable to those of the previous CS. However, CS performed 3 years later revealed a hemorrhagic tumorous lesion in the rectum, measuring approximately 3.0 cm. The lesion was pathologically diagnosed as a poorly-differentiated adenocarcinoma, and surgery was performed (Fig. 4a). Because the tumor was a signet-ring cell carcinoma extending beyond the muscularis propria and showed diffuse positivity for P53 on immunostaining (Fig. 4b, c), UCACD was diagnosed.

Case 5

A 57-year-old woman developed extensive, relapsing-remitting ulcerative colitis at 46 years of age. Clinical remission (1 point on the CAI) had been achieved by treatment with 5-ASA plus azathioprine. At 55 years of age, CS revealed active mucosal inflammation with an invisible vascular pattern, appearing red. At 57 years of age, although CS revealed that the extent of mucosal inflammation was comparable to that shown on the previous CS, a protruded lesion with an irregular surface was detected in the descending colon. The lesion was pathologically diagnosed as high-grade dysplasia, and surgery was performed (Fig. 5a). The surgical findings revealed a protruded lesion measuring 2.0×1.9 cm in the sigmoid colon, which was a well-differentiated adenocarcinoma infiltrating the superficial layer of the muscularis...
Figure 4. a: A hemorrhagic tumor lesion measuring approximately 3 cm was observed in the rectum. b: The tumor was a signet-ring cell carcinoma extending beyond the muscularis propria. Mucosal inflammation in the area other than the tumor lesion was mild. c: The lesion was positive for P53 on immunostaining.

Figure 5. a: A protruding lesion was observed in the sigmoid colon. b: The tumor in the sigmoid colon was a well-differentiated adenocarcinoma that infiltrated the superficial layer of the muscularis propria. c: Immunostaining for P53 showed a diffuse positivity in the lesion.

Discussion

Patients with long-standing ulcerative colitis are at a high risk of developing cancer. According to a meta-analysis performed by Eaden et al., the cumulative incidence of cancer is reported to be 1.6% at 10 years after the onset of ulcerative colitis, 8.3% at 20 years, and 18.4% at 30 years (13). According to the CS findings, significant risk factors for de-
veloping UCACD include the severity of inflammation, endo-
ema findings of a “lead-pipe” colon, inflammatory poly-
posis, stricture, and an intestine showing contraction (14).
All these factors indicate a period of severe inflammation or
prolonged duration of inflammation. Even if the disease ac-
tivity is clinically low, patients whose disease has remained
endoscopically active for a long period are assumed to be at
a high risk of developing cancer because of an increased cu-
mulative duration of inflammation. On the other hand, com-
plete endoscopic resolution of mucosal inflammation is con-
sidered to be a significant factor for lowering the risk (15).
Although clinical remission was achieved in all five patients
encountered, complete resolution of mucosal inflammation
was not achieved in four patients, excluding one (Case 4).
Rosenberg et al. reported that complete resolution of endo-
scopic mucosal inflammation was achieved in only 55% of
149 patients with ulcerative colitis in whom clinical remis-
sion was confirmed (16). In our five patients, because all
had prolonged inflammation during the clinical follow-up
and did not show endoscopic relief of mucosal inflamma-
tion, it is assumed that the risk of cancer remained high.

Treatment with 5-ASA has been reported to reduce the in-
cidence of colorectal cancer/epithelial dysplasia by 49% (17), which suggests the usefulness of 5-ASA for the treat-
ment for UCACD. However, cancer occurred in our five
patients, even though all patients received an oral admini-
stration of 5-ASA. Possible reasons for cancer development
include prolonged duration of inflammation and a lack of
resolution of mucosal inflammation.

In the European Crohn’s and Colitis Organization
(ECCO) Workshop in 2011, it was reported that complete
resolution of mucosal inflammation might contribute to a
decreased incidence of UCACD (18). Many European and
American guidelines recommend performing the first screen-
ing endoscopy in the eighth to tenth year after disease on-
set (19-21). Meanwhile, there is a report that, because ap-
proximately 20% of the cases of UCACD occur within 8
years after the onset of inflammatory bowel disease, the de-
tection of cancer was delayed in approximately 20% of
cases when surveillance was started in the periods recom-
manded by the European and American guidelines (22).
Thus, in the 2012 version of the ECCO guidelines, the rec-
ommended period for initiating surveillance was set earlier,
to 6 to 8 years after onset (23). While we have also set our
guidelines for surveillance colonoscopy according to these
guidelines, our series included a patient who developed can-
cer after only 4 years. Thus, in patients without complete
resolution of mucosal inflammation, careful SC must be in-
itiated in the early phase.

At present, with a mean follow-up of 1.7 years (range, 1
to 2.4 years) after surgery, our five patients are alive without
either recurrence or metastasis.

We herein reported five cases of UCACD. The cumulative
effect of active inflammation in ulcerative colitis appears to
be an important factor closely associated with tumorigenesis.
In order to prevent cancer from developing, appropriate
medical therapy aiming not only for relief of the clinical
symptoms, but also suppression of chronic inflammation and
complete resolution of mucosal inflammation appears to be
necessary.

The authors state that they have no Conflict of Interest (COI).

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