SURVEILLANCE BY MAGNIFYING ENDOSCOPY IN PATIENTS WITH ULCERATIVE COLITIS

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Background: Patients with total or left-sided ulcerative colitis (UC) for more than 10 years have an increased risk of colon cancer. We studied usefulness of magnifying chromoendoscopy for the surveillance of dysplasia and colitic cancer associated with UC.

Methods: From April 2003 through February 2004, 39 patients who had total or left-sided UC for at least 7 years were prospectively enrolled in an endoscopic surveillance program, including target biopsy. All patients were examined by chromoendoscopy and magnifying endoscopy. Sites showing abnormal mucosal surface patterns or pit patterns suggestive of dysplasia underwent biopsy.

Results: Of the 39 patients, 26 had total UC and 13 left-sided UC. The mean time elapsed since the onset of UC was 16.2 ± 5.9 years. Disease activity at examination was remission in 22 patients, mild in 15, and moderate in two. Dysplasia was diagnosed in two patients (three lesions), dysplastic changes were suspected in two (two lesions), and sporadic adenoma was diagnosed in four (five lesions). On endoscopic examination, dysplasia appeared as flat elevated lesions with types III/IV pit patterns. Resected specimens showed low-to-high-grade dysplasia. The four patients presenting with a type III to IV mucosal pit pattern during remission were evaluated as sporadic adenoma on pathological findings.

Conclusions: A combination of chromoendoscopy and magnifying endoscopy is useful for the detection of dysplasia and colitic cancer in patients with UC.

Key words: colitic cancer, dysplasia, magnifying endoscopy, target biopsy, ulcerative colitis.

INTRODUCTION

Colon cancer arising in patients with ulcerative colitis (UC) is referred to as colitic cancer.1 The risk of colitic cancer increases in patients who have had total or left-sided UC for more than 10 years. Colitic cancer is preceded by dysplasia, located adjacent to or far from the tumor.2 As compared with classic colorectal cancer, colitic cancer is characterized by a younger age at onset, poorly differentiated mucinous carcinoma, multiple lesions, diffusely infiltrating (type 4) carcinoma, and a poor prognosis.3 In Japan as well as in other countries, long-term follow up of patients with UC has led to increased reports of colitic cancer.4 Endoscopic surveillance plays an important role in the early diagnosis and treatment of dysplasia and colitic cancer in patients with UC. We report the characteristics and usefulness of magnifying chromoendoscopy for the detection of dysplasia and colitic cancer associated with UC.

MATERIALS AND METHODS

From April 2003 through February 2004, 39 patients who had total or left-sided UC for at least 7 years were prospectively enrolled in an endoscopic surveillance program, including target biopsy. All patients underwent chromoendoscopy and magnifying endoscopy. The number of biopsy specimens obtained was not limited. Most specimens were taken from regions with abnormal mucosal patterns or pit patterns suggestive of dysplasia. Regardless of endoscopic findings, at least one specimen was obtained from the lower rectum (below the peritoneal reflection). Magnifying chromoendoscopy was performed by four specialists who had more than 15 years of experience in endoscopy. Suspected lesions were sprayed with 0.2% indigo carmine or 0.05% crystal violet dye. Findings on magnifying endoscopy were classified according to the pit pattern classification of colorectal tumors proposed by Kudo et al.5,6 Biopsy specimens were sent to a pathology project group and evaluated according to the standardized criteria.

RESULTS

Subjects

A total of 39 patients (15 men and 24 women) were enrolled. The mean age of the patients was 50.0 ± 14.2 years (range, 28–81). The disease type was total UC in 26 patients and left-sided UC in 13. The mean time elapsed since the onset of UC was 16.2 ± 5.9 years (range, 7–30). Disease activity at examination was remission in 22 patients, mild in 15, and moderate in two. On average, 3.6 ± 1.8 (range 1–9) biopsy specimens were obtained per patient, 0.2 from the ascending colon and
Dysplasia was diagnosed in two (three lesions) of the 39 patients, dysplastic changes were suspected in two patients (two lesions), and sporadic adenoma was diagnosed in four patients (five lesions).

**Patient 1: Dysplasia**

A 72-year-old woman had total UC for 8 years. Atrophy and scars were frequently seen in the underlying mucosa. A flat lesion with redness was observed in the sigmoid colon. The border was clearly demarcated on dye spraying. Magnifying endoscopy revealed a type III L to IV pit pattern, with a type V-like pit pattern in some areas (Fig. 1a–c). Biopsy showed low-grade dysplasia at the site, but no overexpression of p53 protein was noted on immunohistochemical staining (Fig. 2a,b). A slightly uneven, flat, elevated lesion was also detected in the distal rectum. Magnifying endoscopy revealed a type III L to IV pit pattern (Fig. 1d,e). Biopsy showed high-grade dysplasia at the site, and overexpression of p53 protein was noted on immunohistochemical staining (Fig. 2c,d).

A total colectomy with a ileostomy was performed. A IIa lesion (3.0 × 2.0 cm) was detected in the sigmoid colon, and a poorly demarcated IIa lesion (1.5 × 1.0 cm) in the rectum (Fig. 3a). Examination of the surgical specimen showed low-grade dysplasia proximal to the IIa lesion in the sigmoid colon, contiguous with a region of high-grade dysplasia distal to the lesion. No overexpression of p53 was observed on immunohistochemical staining (Fig. 4). The lesion in the rectum was low-grade dysplasia, with no overexpression of p53 on immunostaining (Fig. 5).

In this patient, two additional regions of low-grade dysplasia, apart from the low-grade dysplasia detected in the sigmoid colon and rectum on endoscopic examination, were found. These regions were surrounded by sporadic areas showing indefinite for dysplasia (Fig. 3b).

**Patient 2: Suspected dysplasia or sporadic adenoma**

A 44-year-old man had left-sided UC for 17 years. A protruding lesion surrounded by a flat, elevated area was seen in the distal rectum (Fig. 6a–c). Endoscopic mucosal resection was performed, and the surrounding region was treated by argon plasma coagulation.
The protruding area had a type IV pit pattern (Fig. 6d), suggested to be tubulovillous adenoma rather than dysplasia associated with UC on histological examination (Fig. 7a,b). The surrounding flat, elevated area also showed a type IV pit pattern (Fig. 6e), suggesting low-grade dysplasia (Fig. 7d,e). No overexpression of p53 protein was observed in either area on immunostaining (Fig. 7c,f).

The protruding lesion was contiguous with the surrounding flat elevated area, suggesting that the entire region had undergone dysplasia.

Surgery was considered, but the patient was closely observed at his request. Endoscopy 1 year later revealed only scars, with no protruding lesions. There was no histological evidence of dysplasia.

Patient 3: Sporadic adenoma

An 81-year-old woman had total UC for 17 years. A semipendunculated (Isp) polyp was found on the mucosa of the transverse colon during remission. Magnifying endoscopy showed a type IV pit pattern. The lesion was histologically confirmed to be a tubular adenoma, but overexpression of p53 was observed on immunohistochemical staining. A semipendunculated (Isp) polyp was also found distal to the first lesion. Magnifying endoscopy revealed a type IV pit pattern (Fig. 8a,b). Histologically, the lesion was a tubulovillous adenoma. Immunohistochemical staining showed overexpression of p53 (Fig. 8c–e).

Of the four patients with sporadic adenoma, only this patient showed increased expression of p53 in some regions. The other three had no overexpression of p53.

Patient 4: Typical regenerative hyperplastic changes

Flat, mucosal changes were localized in the sigmoid colon (Fig. 9a). Magnifying endoscopy revealed a canal-like pattern
We refer to this pattern as a ripple-like pattern, typical of the regenerative hyperplastic changes associated with UC (Fig. 9c,d).

**DISCUSSION**

The presence of an inflamed mucosa in patients with UC often precludes the early detection of dysplasia and colitic cancer on endoscopy. A study group organized by the Ministry of Health, Labor, and Welfare has studied efficient ways for disease surveillance.

In patients with UC, the risk of dysplasia or cancer increases with the duration of disease. Both dysplasia and colitic cancer occur most frequently in patients with total or left-sided UC. Therefore, patients who have total or left-sided UC for 7 years or longer should be examined according to a predetermined surveillance program for UC.

Surveillance should be performed once a year, when the disease is in remission if possible. However, the rate of scheduled surveillance at our hospital is about 56% because many young patients refuse to undergo examinations and surveillance is impractical during disease flare-ups. One of our future tasks is to study ways to increase the rate of surveillance for UC.

Overseas, random biopsy has been recommended for surveillance in patients with UC. With this procedure, biopsy specimens are obtained from various sites of the colon at 10-cm intervals, regardless of endoscopic findings. This method is considered useful for the detection of scirrhous-type cancer, but has the disadvantage of requiring many unnecessary biopsies. We therefore perform target biopsy to obtain specimens mainly from lesions suspected to be dysplasia or cancer on endoscopic examination. Endoscopically, most cases of dysplasia or early colitic cancer are likely to be associated with flat mucosal lesions or protruding lesions referred to as ‘dysplasia-associated lesions or masses’ characterized by granular or nodular elevated mucosa or flat protrusions. Such lesions generally appear red on conventional endoscopy, and their diagnosis is facilitated by spraying suspected lesions with dyes such as indigo carmine. The diagnostic accuracy of surveillance can be further enhanced by biopsy and

(Fig. 9b)
evaluation of pit or surface patterns by magnifying endoscopy after spraying lesions with crystal violet or methylene blue dye.\textsuperscript{10–12} Kiesslich \textit{et al.}\textsuperscript{11} reported that using chromoendoscopy, a differentiation of non-neoplastic changes (pit patterns I and II) and neoplastic changes (pit patterns III–V) was possible with a high sensitivity and specificity of 93\% in UC. In our previous study,\textsuperscript{13} 10 regions of dysplasia in seven patients and five colitic cancers in four patients were examined by magnifying endoscopy. Six regions of dysplasia showed coarse III\textsubscript{S} type III\textsubscript{L}–type pits, and four showed IV-type pits. The superficial depressed-type (II\textsubscript{c}) early cancer had a III\textsubscript{S} pit pattern. Two early cancers showed III\textsubscript{L}–type pits, and two showed IV-type pits. Biopsy of regions with tumorous pits showed dysplasia and colitic cancer. In contrast, biopsy of regions with non-tumorous pits showed no evidence of dysplasia or colitic

\textbf{Fig. 6.} (a–c) Patient 2. A protruding lesion surrounded by a flat elevated area was found in the rectum below the peritoneal reflection. (d) After spraying the lesion with crystal violet, magnifying endoscopy revealed a type IV pit pattern in the highly elevated area. (e) Magnifying endoscopy showed a type IV pit pattern in the surrounding flat elevated area.

\textbf{Fig. 7.} (a,b) The protruding lesion appeared to be a tubulovillous adenoma on endoscopic mucosal resection (EMR). (c) No overexpression of p53 was noted at the same region. (d,e) Low-grade dysplasia was found on EMR of the flat, elevated area. (f) No overexpression of p53 was noted on immunostaining of the region.
cancer. Histopathological to regenerative hyperplastic changes correspond to a pit pattern of type I to II according to Kudo’s classification on magnifying chromoendoscopy, whereas dysplasia or colitic cancer indicates type III to IV. In our study, dysplasia or sporadic adenoma was found at sites showing a type III to IV pit pattern. Inflammatory or regenerative hyperplastic change mainly showed type I to II pit pattern. However, histological examination of biopsy specimens of the mucosa in active colitis revealed findings difficult to distinguish from those of dysplasia, even when the pit pattern was type I to II. Re-examination during remission was therefore considered necessary. It is difficult to distin-

Fig. 8. (a,b) Patient 3. A semipendunculated (Isp) polyp was found in the transverse colon. Magnifying endoscopy revealed a type IV pit pattern. (c,d) Histologically, the lesion was a tubulovillous adenoma. (e) Overexpression of p53 was noted on immunostaining of the same site.

Fig. 9. (a) Patient 4. A flat, localized mucosal change was seen in the sigmoid colon. (b) Magnifying endoscopy revealed a canal-like (ripple-like) pattern. (c,d) Histologically, regenerative hyperplastic changes were found.
guish dysplasia from sporadic adenoma solely on the basis of pit patterns, but the gaps between pits appear to be larger in dysplasia. Accurate diagnosis requires a comprehensive evaluation of inflammatory changes and biopsy findings in both elevated areas and the surrounding mucosa, as well as an assessment of the sites of proliferation zones and the expression of p53 protein on immunohistochemical staining.

To detect dysplasia, abnormal regions should be identified on conventional endoscopy and then be sprayed with dye to more clearly define potential lesions. Dysplasia is suspected if tumorous pits are observed on magnifying endoscopy. Biopsy of the region can confirm the diagnosis. We regard this to be a rational and efficient technique for the detection of dysplasia.

In conclusion, our study suggested that a combination of chromoendoscopy, magnifying endoscopy, and target biopsy is useful for the detection of dysplasia and colitic cancer in patients with UC, with a considerable reduction in the number of biopsy specimens as compared with random biopsy.

REFERENCES