Intestinal Endometriosis: Clinicopathologic Analysis of 15 Cases Including a Case of Endometrioid Adenocarcinoma

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Received: July 4, 2008
Accepted: December 16, 2008

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Endometriosis is defined as the growth of endometrial glands or stroma outside the uterine cavity.1 Intestinal endometriosis is relatively uncommon, occurring in 5% of women with endometriosis,1,2 and the involved sites include the rectum, sigmoid, appendix, terminal ileum, and cecum, in descending order of frequency.3 Patients usually experience abdominal or rectal pain, tenesmus, constipation, diarrhea, loose stools, and hematochezia, depending on the site involved.1,2 Because many patients present with gastrointestinal symptoms, radiologic examination or endoscopy of the intestinal tract is usually performed at the initial presentation,4 often leading to misdiagnoses as various inflammatory lesions or tumors of the intestine based on the findings of obstructive or infiltrative masses.2,5,6 We therefore sought to identify the pathologic characteristics of intestinal endometriosis by assessing the histopathologic and immunohistochemical properties of endoscopic biopsy and resected specimens. Since diagnosis of intestinal endometriosis in the resected specimens is rarely a problem, we particularly focused on endoscopic biopsy specimens.

Background: Since many patients with intestinal endometriosis present with gastrointestinal symptoms without a history of endometriosis, endoscopic examination of the intestinal tract is initially performed, often leading to a misdiagnosis. Methods: We reviewed the clinicopathologic findings of 18 samples from 15 patients with intestinal endometriosis who underwent endoscopic biopsy and/or surgical resection to identify diagnostically helpful findings. Results: All 7 biopsy specimens displayed relatively well-defined submucosal lesions, with non-mucinous glands lined by ciliated epithelium and surrounding cellular stroma containing spiral arteriole-like blood vessels. The stroma was immunopositive for CD10 in all cases. All but one specimen exhibited immunopositivity for ER and PR in both glandular and stromal components. In contrast to the overlying normal colonic mucosa, glandular epithelium with endometriosis was immunopositive for cytokeratin (CK) 7, but immunonegative for CK20 in all cases. Three cases were associated with adenocarcinoma in the same or different segments; specifically, two primary rectal adenocarcinomas and one endometrioid adenocarcinoma arising from endometriosis. Conclusions: The characteristic features of endometrial glands and stroma, including non-mucinous glands without goblet cells, ciliated columnar epithelium, and cellular stroma with spiral arterioles, facilitate the accurate diagnosis of intestinal endometriosis, which can be confirmed by immunohistochemical staining.

Key Words: Endometriosis; Intestine; Endometrioid adenocarcinoma

MATERIALS AND METHODS

The surgical pathology files of the Department of Pathology, Asan Medical Center (Seoul, Korea), contained 18 verified samples of intestinal endometriosis from 15 patients between 1996 and 2006. Among these patients, 4 had been diagnosed with intestinal endometriosis based on endoscopic biopsy alone, one had surgical resection after repeated endoscopic biopsies (case 5), and 10 underwent surgical resection only (cases 1-4 and 6-11). The gross and microscopic findings and the patients’ clinical records were reviewed in all cases.

In 17 samples, immunohistochemical staining was performed on formalin-fixed and paraffin-embedded tissue sections using an autostainer (Ventana Medical Systems Inc., Tucson, AZ, USA). The primary antibodies used were cytokeratin (CK) 7 (1:200 dilution; DAKO, Glostrup, Denmark), CK20 (1:200 dilution; DAKO), CD10 (1:50 dilution; NOVO, Newcastle, UK), estrogen receptor (ER, 1:400 dilution; NeoMarkers, Fremont, CA, USA), and progesterone receptor (PR, 1:400 dilution; NeoMark-
After incubation with the primary antibodies, immunodetection was performed with biotinylated anti-mouse immunoglobulin followed by peroxidase-labeled streptavidin, using the LSAB kit (DAKO) and 3,3′-diaminobenzidine chromogen as the substrate. An endogenous biotin blocking kit was used to reduce non-specific immunopositivity (Ventana Medical Systems Inc.). Diaminobenzidine was used as a chromogen, and tissues were counterstained with hematoxylin.

### RESULTS

#### Clinical findings

The median patient age at the time of diagnosis was 41 years (Table 1). The presenting clinical symptoms included abdominal pain (8/15 [53.3%]), hematochezia (6/15 [40.0%]), tenesmus (2/15 [13.3%]), and constipation (2/15 [13.3%]). Two patients (cases 4 and 10) exhibited no clinical symptoms, but intestinal endometriosis was incidentally detected during surgery for a villotubular adenoma and an infertility work-up, respectively. Based on radiologic and clinical findings, 5 patients (33.3%) were diagnosed with colon cancer, 5 patients (33.3%) with ovarian cysts, 3 patients (20%) with submucosal tumors of the large intestine, 1 patient (6.7%) with invasion of ovarian cancer, and 1 patient (6.7%) with appendicitis. Endometriosis was located in the rectum in 8 (53.3%) patients, the appendix in 6 patients (40.0%), and the sigmoid colon in 1 patient (6.7%). In 8 patients (53.3%), intestinal endometriosis was associated with histologically-proven ovarian endometriosis, and 1 patient (6.7%) with adenomyosis, while the remaining 6 patients had no history of endometriosis.

#### Table 1. Clinicopathological and immunohistochemical findings in patients with intestinal endometriosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Symptoms</th>
<th>Clinical impression</th>
<th>Associated endometriosis</th>
<th>Procedure</th>
<th>Location</th>
<th>Involved layers</th>
<th>ER/PR/CD10/CK7/CK20</th>
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<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Constipation</td>
<td>Colon cancer</td>
<td>Ovarian endometriosis</td>
<td>TAH, BSO, Appendectomy, Appendectomy, Segmentectomy</td>
<td>Appendix</td>
<td>S, M</td>
<td>+/-/+/+/-/+-/-</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>Abdominal pain, Tenesmus, Hematochezia</td>
<td>Colon cancer</td>
<td>-</td>
<td>LAR, Appendectomy</td>
<td>Rectum</td>
<td>P</td>
<td>+/-/+/+/-/+-/-</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>Constipation, Hematochezia</td>
<td>Colon cancer</td>
<td>Ovarian endometriosis</td>
<td>LAR</td>
<td>Rectum</td>
<td>P, M</td>
<td>+/-/+/+/-/+-/-</td>
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<tr>
<td>4</td>
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<td>-</td>
<td>LAR</td>
<td>Rectum</td>
<td>P</td>
<td>+/-/+/+/-/+-/-</td>
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<tr>
<td>5</td>
<td>36</td>
<td>Tenesmus, Dyspareunia</td>
<td>Submucosal tumor</td>
<td>-</td>
<td>Biopsy (x2), LAR, TAH</td>
<td>Rectum</td>
<td>P, M, Sm</td>
<td>+/-/+/+/-/+-/-</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Abdominal pain</td>
<td>Appendicitis</td>
<td>Ovarian endometriosis</td>
<td>Appendectomy RSO, LOC, Appendectomy, Appendectomy</td>
<td>Appendix</td>
<td>S, M</td>
<td>+/-/+/+/-</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Abdominal pain</td>
<td>Ovary cyst</td>
<td>Ovarian endometriosis</td>
<td>Appendectomy LOC, Appendectomy</td>
<td>Appendix</td>
<td>S, M, NT</td>
<td>+/-/+/+/-/+-/-</td>
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<td>Ovary cyst</td>
<td>Ovarian endometriosis</td>
<td>Appendectomy BOC, Appendectomy</td>
<td>Appendix</td>
<td>S, M</td>
<td>+/-/+/+/-/+-/-</td>
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<tr>
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<td>Ovarian endometriosis</td>
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<tr>
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<tr>
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<td>41</td>
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<td>Ovary cyst</td>
<td>Ovarian endometriosis</td>
<td>Appendix</td>
<td>S, M, Sm</td>
<td>+/-/+/+/-/+-/-</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>41</td>
<td>Abdominal pain, Hematochezia</td>
<td>Submucosal tumor</td>
<td>Adenomyosis</td>
<td>Biopsy</td>
<td>Rectum</td>
<td>Sm</td>
<td>+/-/+/+/-/+-/-</td>
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<td>45</td>
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<td>-</td>
<td>Biopsy</td>
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<td>Sm</td>
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<td>47</td>
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<td>Invasion</td>
<td>Ovarian endometriosis</td>
<td>Biopsy</td>
<td>Rectum</td>
<td>Sm</td>
<td>+/-/+/+/-/+-/-</td>
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<tr>
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<td>38</td>
<td>Abdominal pain</td>
<td>Submucosal tumor</td>
<td>-</td>
<td>Biopsy (x2)</td>
<td>Rectum</td>
<td>Sm</td>
<td>+/-/+/+/-/+-/-</td>
</tr>
</tbody>
</table>

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LAR, low anterior resection; RSO, right salpingo-oophorectomy; LOC, left ovarian cystectomy; BOC, bilateral ovarian cystectomy; LSO, left salpingo-oophorectomy; ROC, right ovarian cystectomy; P, perirectal soft tissue; S, serosa; M, proper muscle layer; Sm, submucosa; NT, not tested.
Pathologic findings

Endoscopic biopsy specimens

Among the 4 patients diagnosed using endoscopic biopsy alone, 1 was clinically suspected to have colon cancer, 2 with submucosal tumors, and 1 with colonic invasion of ovarian cancer. Seven endoscopic biopsy specimens were obtained from 5 patients (cases 5, 12-15). Each specimen contained 2-5 pieces (average, 3.5) of colonoscopic-biopsied mucosa. Endometriotic foci were relatively well-delineated from the surrounding normal intestinal mucosa (Fig. 1A). All 7 biopsy specimens were characterized by non-mucinous glandular structures lined by ciliated columnar epithelium and surrounded by cellular stroma containing abundant thin-walled vasculature (Fig. 1B). Glands were irregular and larger in shape and size compared to the adjacent colonic mucosa, and lined by tall columnar epithelium cells with elongated nuclei showing regular vertical orientation. Goblet cells were absent, in contrast to the adjacent normal colonic mucosa. The epithelium displayed immunopositivity for CK7 (Fig. 2A), but immunonegativity for CK20 (Fig. 2B), in contrast to overlying normal colonic mucosa, which was negative for CK7 and positive for CK20. All samples, periglandular stroma was distinguished from the lamina propria of normal colonic mucosa by the presence of short, spindle-shaped cells with inconspicuous cytoplasm and abundant small vasculature. The stroma was immunopositive for CD10 in the endometriotic foci, but negative in the lamina propria of the colon (Fig. 2C). All but one case (case 12) showed diffuse immunopositivity for ER in the endometrial glands and stroma (Fig. 2D), but endometriosis was confirmed in an ER- and PR-negative case (case 12) based on the strong immunopositivity for CD10 in the stroma.

Surgically-resected specimens

Among the 11 surgically-resected cases, the pre-operative diagnoses were as follows: colon cancer in 4 patients, submucosal tumors (such as a gastrointestinal tumor) in 1 patient, acute appendicitis in 1 patient, and ovarian cysts in 5 patients. Grossly, all 11 specimens had multifocal hemorrhagic spots on the serosal surfaces. Apart from 4 cases with adenocarcinomas or villotubular adenomas, the overlying mucosa of the resected specimens remained intact. Two patients (18.2%) displayed serosal surface involvement only, 7 patients (63.6%) showed involvement of the serosa and muscle layers, and 2 patients (18.2%) had involvement of the serosa to the submucosa. In cases 5 and 11, the intestinal walls were irregularly thickened and fibrotic. Moreover, in case 5, focal cystic changes containing gray-brown material were identified in the thickened wall.

Intestinal endometriosis was associated with adenocarcinoma in the same segment in 2 patients (cases 2 and 3) and in different segments in 1 patient (case 1). In cases 2 and 3, lesions of endometriosis and adenocarcinoma involved different layers of the same segment, and 1 patient (case 3) contained an endometrioid adenocarcinoma arising from endometriosis in the same segment involving the entire thickness of the rectal wall from the mucosa to the perirectal soft tissue.

Clinical and pathological findings of the latter closely mimicked those of primary colorectal cancer, with ulceration of the overlying mucosa (Fig. 3A, B), and the neoplastic glands focal-

![Fig. 1. Endoscopic biopsy specimen showing rectal endometriosis. (A) Endometriotic focus in the submucosa (arrows) is relatively well delineated from the surrounding normal colonic mucosa. (B) Non-mucinous ciliated epithelium and cellular stroma containing spiral arteriole-like blood vessels are characteristic findings.](image-url)
ly contained mucinous epithelium (Fig. 3C). However, the mass grew into the cystic space of endometriosis lined by endometriotic glands and stroma. The epicenter of the tumor was located in the deep muscle layer and perirectal soft tissue with only a small mucosal opening (Fig. 3A, B). In contrast to primary colorectal adenocarcinoma and overlying normal rectal mucosa, endometrioid adenocarcinoma was strongly immunopositive for ER (Fig. 3D) and CK7 (Fig. 3E), but negative for CK20.

**DISCUSSION**

Clinically, intestinal endometriosis can simulate irritable bowel syndrome, acute appendicitis, inflammatory bowel disease, diverticulitis, submucosal tumors, or intestinal carcinoma. While intestinal endometriosis is frequently associated with pelvic endometriosis, gastrointestinal symptoms may be the first manifestation of the disease. In our series, 4 patients (cases 5, 6, 13, and 15) presented with intestinal symptoms, such as abdominal pain, tenesmus, and hematochezia, with no history of endometriosis. Therefore, intestinal endometriosis should be considered during the differential diagnosis of intestinal lesions. While intestinal endometriosis occurs more frequently in women of reproductive age, this factor is not critical since disease onset in 2 of our patients occurred after 50 years of age, and one had surgical menopause 10 years before presentation.

Adenocarcinoma can arise in endometriosis, albeit rarely. The histopathologic criteria for the diagnosis of primary adenocarcinoma arising in endometriosis include the following: 1) clear evidence of endometriosis within close proximity to the tumor, 2) no other primary site of adenocarcinoma, and 3) histologic appearance similar to native endometrium of the uterus. Adenocarcinoma in endometriosis is easily confused with primary colorectal carcinoma since tumor cells often contain mucin.
secretion epithelium. However, the growth patterns are usually different, as in our case. The epicenter of the tumor is usually outside the intestinal wall, but these tumors ultimately invade the intestinal wall. Compared with primary colorectal carcinoma, the extent of mucosal involvement or the mucosal opening is generally smaller (Fig. 3A). Differentiation between adenocarcinoma arising in endometriosis and primary colorectal carcinoma is crucial owing to better prognosis of the former and distinct treatment plans.

In conclusion, characteristic features of endometrial glands and stroma, including non-mucinous glands without goblet cells, ciliated columnar epithelium, and cellular stroma with spiral arterioles, are helpful in the diagnosis of intestinal endometriosis, which can be confirmed by immunohistochemical staining.
CK7, CK20, ER, PR, and CD10.\textsuperscript{11-19}

REFERENCES


