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

Heejin Lee · Kyu-Rae Kim

Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Corresponding Author
Kyu-Rae Kim, M.D.
Department of Pathology, Asan Medical Center,
University of Ulsan College of Medicine, 388-1
Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel: 02-3010-4514
Fax: 02-472-7898
E-mail: krkim@amc.seoul.kr

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

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.

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-

ers). 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

Case No.	Age	Symptoms	Clinical impression	Associated endometriosis	Procedure	Location	Involved layers	ER/PR/CD10/CK7/CK20
1	50	Constipation	Colon cancer	Ovarian endometriosis	TAH, BSO, Appendectomy, Segmentectomy	Appendix	S, M	+/+/+/+/–
2	43	Abdominal pain, Tenesmus, Hematochezia	Colon cancer	–	LAR, Appendectomy	Rectum	P	+/+/+/+/–
3	53	Constipation, Hematochezia	Colon cancer	Ovarian endometriosis	LAR	Rectum	P, M	+/+/+/+/–
4	42	None	Colon cancer	–	LAR	Rectum	P	+/+/+/+/–
5	36	Tenesmus, Dyspareunia	Submucosal tumor	–	Biopsy (x2), LAR, TAH	Rectum	P, M, Sm	+/+/+/+/–
6	42	Abdominal pain	Appendicitis	–	Appendectomy	Appendix	S, M	+/+/+/+/–
7	36	Abdominal pain	Ovary cyst	Ovarian endometriosis	RSO, LOC, Appendectomy	Appendix	S, M	NT
8	39	Abdominal pain	Ovary cyst	Ovarian endometriosis	BOC, Appendectomy	Appendix	S, M	+/+/+/+/–
9	31	Abdominal pain	Ovary cyst	Ovarian endometriosis	LOC, Appendectomy	Appendix	S, M	+/+/+/+/–
10	35	None	Ovary cyst	Ovarian endometriosis	LSO, ROC, Appendectomy	Appendix	S, M	+/+/+/+/–
11	41	Abdominal pain, Hematochezia	Ovary cyst	Ovarian endometriosis	LSO, Appendectomy, Segmentectomy	Sigmoid	S, M, Sm	+/+/+/+/–
12	41	Abdominal pain, Hematochezia	Submucosal tumor	Adenomyosis	Biopsy	Rectum	Sm	–/–/+/+/–
13	45	Hematochezia	Colon cancer	–	Biopsy	Rectum	Sm	+/+/+/+/–
14	47	Hematochezia	Invasion ovary cancer	Ovarian endometriosis	Biopsy	Rectum	Sm	+/+/+/+/–
15	38	Abdominal pain	Submucosal tumor	–	Biopsy (x2)	Rectum	Sm	+/+/+/+/–

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. In 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.

Endometriosis specimens associated with adenocarcinoma

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-
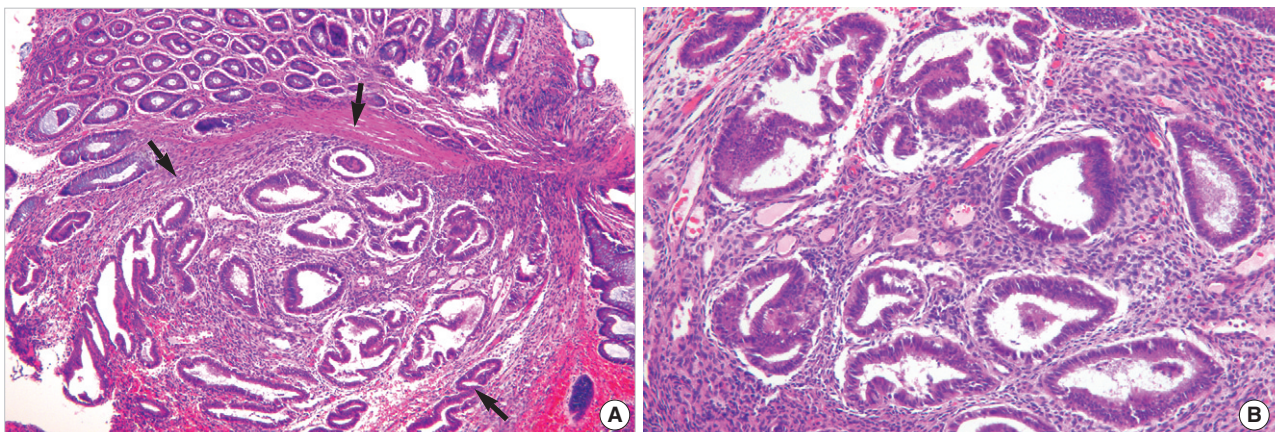

Fig. 1. Endoscopic biopsy specimen showing rectal endometriosis. (A) Endometriotic focus in the submucosa (arrows) is relatively well delineated from the surrounding normal colonic mucosa. (B) Non-mucinous ciliated epithelium and cellular stroma containing spiral arteriole-like blood vessels are characteristic findings.
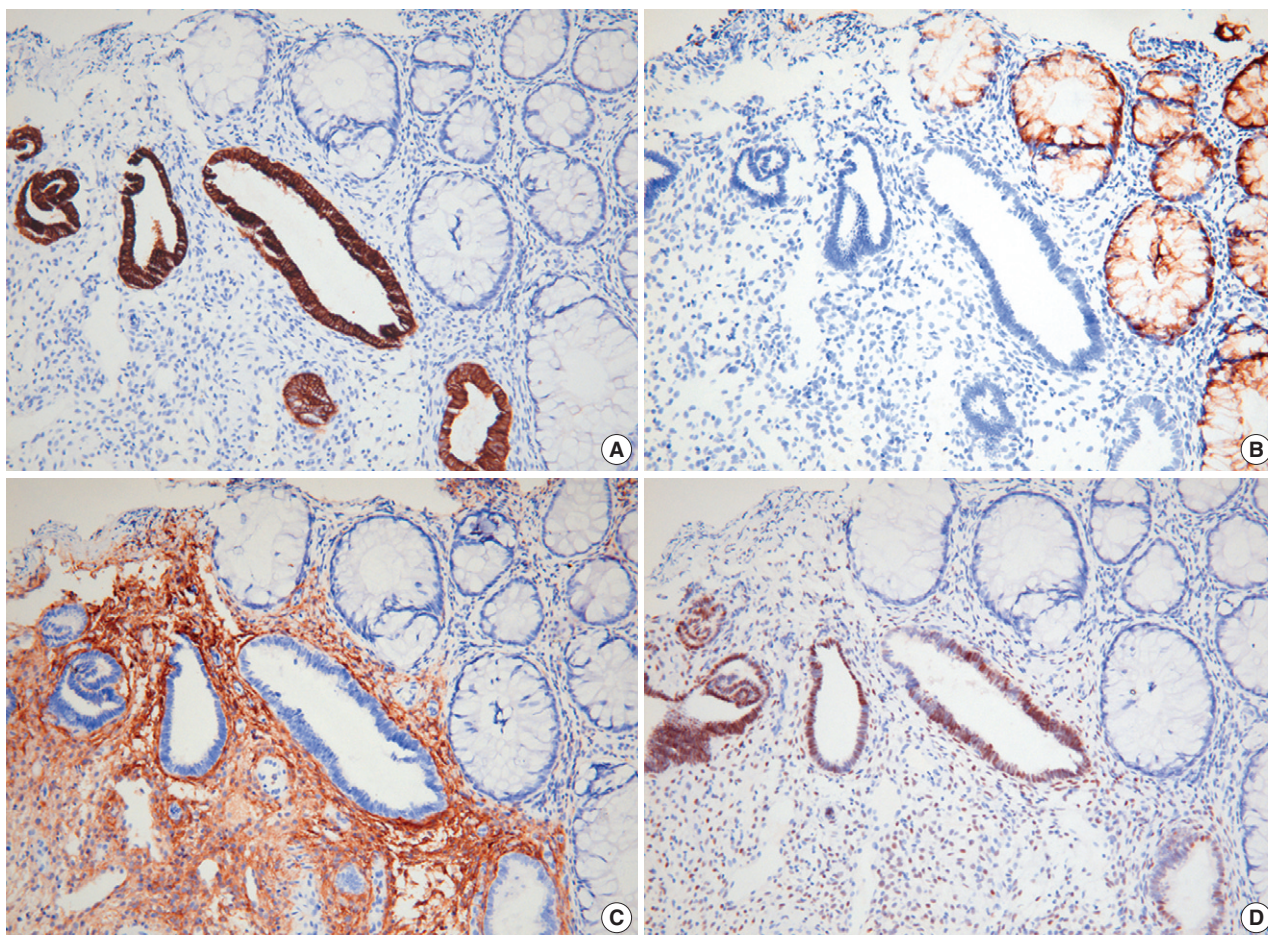
Fig. 2. Immunohistochemical findings in intestinal endometriosis. Endometrial glands are immunopositive for cytokeratin 7 (A) and negative for cytokeratin 20 (B), in contrast to the surrounding normal colonic epithelium. (C) Dense periglandular stroma shows strong immunopositivity for CD10 antibody. (D) Glandular epithelium and/or stroma are immunopositive for ER, in contrast to the surrounding colonic mucosa.

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.[7,8] While intestinal endometriosis is frequently associated with pelvic endometriosis,[9] gastrointestinal symptoms may be the first mani-

festation of the disease.[3] 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.[4,10,11] 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.[4,6,10-12] 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-
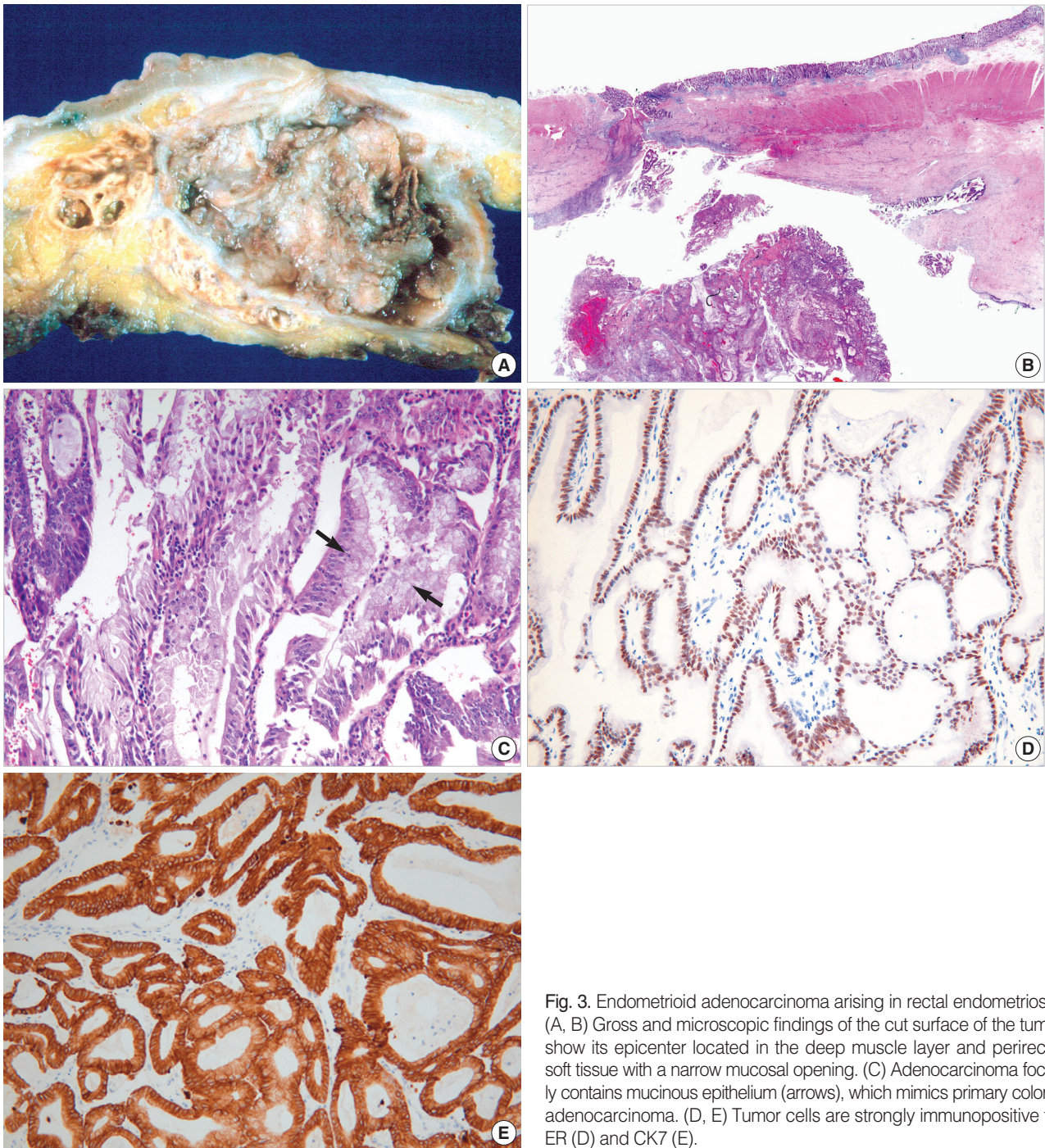
Fig. 3. Endometrioid adenocarcinoma arising in rectal endometriosis. (A, B) Gross and microscopic findings of the cut surface of the tumor show its epicenter located in the deep muscle layer and perirectal soft tissue with a narrow mucosal opening. (C) Adenocarcinoma focally contains mucinous epithelium (arrows), which mimics primary colonic adenocarcinoma. (D, E) Tumor cells are strongly immunopositive for ER (D) and CK7 (E).

secreting epithelium. However, the growth patterns are usually different, as in our case.[4] 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 carci-

noma is crucial owing to better prognosis of the former and distinct treatment plans.[13]

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 for

CK7, CK20, ER, PR, and CD10.[14-19]

REFERENCES

1. Robboy JR, Anderson MC, Russell P. Endometriosis. In: Robboy JR, Anderson MC, Russell P, eds. Pathology of the female reproductive tract. London: Churchill Livingstone, 2002; 445-70.

2. Kanthimathinathan V, Elakkary E, Bleibel W, Kuwajerwala N, Conjeevaram S, Tootla F. Endometrioma of the large bowel. Dig Dis Sci 2007; 52: 767-9.

3. Clement PB. Diseases of the peritoneum. In: Kurman RJ, ed. Blaustein's pathology of the female genital tract. 5th ed. New York: Springer-Verlag, 2002; 761-2.

4. Hoang CD, Boettcher AK, Jessurun J, Pambuccian SE, Bullard KM. An unusual rectosigmoid mass: endometrioid adenocarcinoma arising in colonic endometriosis: case report and literature review. Am Surg 2005; 71: 694-7.

5. Varras M, Kostopanagiotou E, Katis K, Farantos C, Angelidou-Manika Z, Antoniou S. Endometriosis causing extensive intestinal obstruction simulating carcinoma of the sigmoid colon: a case report and review of the literature. Eur J Gynaecol Oncol 2002; 23: 353-7.

6. Yantiss RK, Clement PB, Young RH. Neoplastic and pre-neoplastic changes in gastrointestinal endometriosis: a study of 17 cases. Am J Surg Pathol 2000; 24: 513-24.

7. Remorgida V, Ferrero S, Fulcheri E, Ragni N, Martin DC. Bowel endometriosis: presentation, diagnosis, and treatment. Obstet Gynecol Surv 2007; 62: 461-70.

8. Yantiss RK, Clement PB, Young RH. Endometriosis of the intestinal tract: a study of 44 cases of a disease that may cause diverse challenges in clinical and pathologic evaluation. Am J Surg Pathol 2001; 25: 445-54.

9. Redwine DB. Ovarian endometriosis: a marker for more extensive pelvic and intestinal disease. Fertil Steril 1999; 72: 310-5.

10. Jones KD, Owen E, Berresford A, Sutton C. Endometrial adenocarcinoma arising from endometriosis of the rectosigmoid colon. Gynecol Oncol 2002; 86: 220-2.

11. Petersen VC, Underwood JC, Wells M, Shepherd NA. Primary endometrioid adenocarcinoma of the large intestine arising in colorectal endometriosis. Histopathology 2002; 40: 171-6.

12. Slavin RE, Krum R, van Dinh T. Endometriosis-associated intestinal tumors: a clinical and pathological study of 6 cases with a review of the literature. Hum Pathol 2000; 31: 456-63.

13. Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol 2007; 14: 241-60.

14. Sumathi VP, McCluggage WG. CD10 is useful in demonstrating endometrial stroma at ectopic sites and in confirming a diagnosis of endometriosis. J Clin Pathol 2002; 55: 391-2.

15. Groisman GM, Meir A. CD10 is helpful in detecting occult or inconspicuous endometrial stromal cells in cases of presumptive endometriosis. Arch Pathol Lab Med 2003; 127: 1003-6.

16. McCluggage WG, Oliva E, Herrington CS, McBride H, Young RH. CD10 and calretinin staining of endocervical glandular lesions, endocervical stroma and endometrioid adenocarcinomas of the uterine corpus: CD10 positivity is characteristic of, but not specific for, mesonephric lesions and is not specific for endometrial stroma. Histopathology 2003; 43: 144-50.

17. Fujishita A, Nakane PK, Koji T, *et al.* Expression of estrogen and progesterone receptors in endometrium and peritoneal endometriosis: an immunohistochemical and in situ hybridization study. Fertil Steril 1997; 67: 856-64.

18. Bergqvist A, Ferno M. Estrogen and progesterone receptors in endometriotic tissue and endometrium: comparison according to localization and recurrence. Fertil Steril 1993; 60: 63-8.

19. Loy TS, Calaluce RD, Keeney GL. Cytokeratin immunostaining in differentiating primary ovarian carcinoma from metastatic colonic adenocarcinoma. Mod Pathol 1996; 9: 1040-4.