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Original article

Intestinal metaplasia of appendiceal endometriosis is not uncommon and may mimic appendiceal mucinous neoplasm

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ABSTRACT

Endometriosis of the appendix can be an incidental finding or a cause of appendicitis, intussusception, perforation or retention mucocele. Intestinal metaplasia of appendiceal endometriosis may occur, which can lead to a misdiagnosis of low-grade appendiceal mucinous neoplasm. On a retrospective search of the pathology database from 2001 to 2015, we identified 78 appendiceal endometriosis cases and intestinal metaplasia was present in 10/78 (13%) cases. In most of the cases (90%), the foci of intestinal metaplasia were mainly localized close to the mucosa. Intestinal and endometrial hybrid glands were present in 9/10 (90%) cases. These cases were often associated with marked appendiceal distortion, luminal obliteration and mass formation, causing concern for a mucinous neoplasm clinically and pathologically. Our findings indicate that intestinal metaplasia in appendiceal endometriosis is not an uncommon phenomenon, which can be mistaken for a mucinous neoplasm. Endometriosis should be kept in mind when a diagnosis of appendiceal mucinous neoplasm is made, especially in a young woman with a clinical history of endometriosis.

1. Introduction

The gastrointestinal tract is a common location for extra-pelvic endometriosis [1]. Involvement of the gastrointestinal tract is seen in around 15–37% patients with pelvic endometriosis [2]. Appendiceal involvement by endometriosis is relatively uncommon, and in one study of 543 female appendectomy specimens, endometriosis was only found in 2 cases (0.36%) [3]. Another study found 14 cases of appendiceal endometrosis in 2284 female appendectomy specimens (0.61%) [4]. Appendiceal endometriosis can have diverse clinical presentations, ranging from mass lesions, intussusception, acute or cyclical pain, and perforation of the appendix [5]. Such clinical presentations can be a source of confusion to the clinician and pathologists. This situation can be further complicated on histopathologic examination if there are metaplastic changes in the endometriotic glands. A variety of metaplastic changes have been described in endometriosis, including ciliated, eosinophilic, hobnail, and mucinous metaplasia. Mucinous metaplasia is commonly of endocervical type but can also be intestinal or goblet cell type [6]. Mai et al. were the first to report intestinal metaplasia in endometriosis involving the appendix in 1999 [7]. Since then, several studies have attested this phenomenon [5,8]. Intestinal metaplasia has not been reported frequently in endometriosis involving the gastrointestinal tract, other than in the appendix. Recognizing this phenomenon in the appendix is especially important because of the potential to misdiagnose it as a low grade appendiceal mucinous neoplasm [5]. Also, endometriosis at other sites has been associated with neoplasms, and this possibility must be considered when dealing with unusual neoplasms in the appendix as well [9].

The aim of this study was to identify the incidence of intestinal metaplasia in endometriosis involving the appendix. We also sought to study if there are any common pathologic features which might help to differentiate it from appendiceal mucinous neoplasm.

2. Methods

On a retrospective search of the pathology database from 2001 to 2015, we found 78 cases of endometriosis involving the appendix. Hematoxylin and eosin (H&E) stained slides for all the cases were reviewed for epithelial metaplasia within endometriosis using the criteria suggested by Hendrickson and Kempson [10]. Only cases with definitive intestinal metaplasia, which is defined by the presence of mucin-producing columnar cells and goblet cells, were included for the study. For each selected case, the age, clinical presentation, surgery procedure, presence of endometriosis at

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Table 1
Clinical and pathologic features of appendiceal endometriosis.

Cases	Age (yrs)	Presentation	Procedure	Endometriosis at other sites	Extent of endometriosis in appendix	Focality of IM	Location of IM
1	33	31 wks pregnant, RLQ pain	Right hemicolectomy	–	Extensive,	Multifocal	Submucosal
2	33	Ovarian cyst	Appendectomy + salpingo-oophorectomy	Fallopian tubes	Extensive,	Multifocal	Submucosal
3	52	2 cm RLQ mass	Appendectomy +cecetomy	–	Extensive	Multifocal	Submucosal
4	29	Pelvic pain	Appendectomy	Peritoneum	Extensive	Multifocal	Submucosal
5	30	RLQ pain	ileocecetomy	–	Moderate	Multifocal	Muscularis propria
6	39	Pelvic mass	Appendectomy + TAHBSO	B/L ovaries	Moderate	Multifocal	Submucosal
7	33	RLQ pain, mass	Right hemicolectomy	Pelvic wall	Extensive	Multifocal	Submucosal
8	24	24 wks pregnant, RLQ pain	Appendectomy	–	Extensive	Multifocal	Submucosal
9	49	Left adnexal mass	Cecectomy	Ovary	Moderate	Multifocal	Submucosal
10	48	3 cm RLQ mass	Right hemicolectomy	–	Extensive	Multifocal	Submucosal

RLQ – Right lower quadrant, TAHBSO – total abdominal hysterectomy with bilateral salpingo-oophorectomy.

other sites and follow up were recorded. For each case reviewed, the following pathologic characteristics were documented: extent and location of endometriosis, focality of intestinal metaplasia, type of cells present (goblet, Paneth, neuroendocrine), and presence or absence of endometrial stroma. Immunohistochemistry for cytokeratin (CK) 7 (Dako, OVTL, 1:400), CK20 (Dako, KS20.8, 1:400), CDX2 (Biocare, Clone 88, neat), Estrogen receptor ER (Cell marque, SP-1, 1:50) and CD10 (Vector, 56C6, 1:80) were also performed in challenging cases.

3. Results

The key clinical and pathologic findings are summarized in Table 1.

3.1. Clinical findings

Intestinal metaplasia was found in 13% (10/78) of the appendiceal endometriosis cases, with an age range from 24 to 52 years (average 37 years). Of the 10 patients with intestinal metaplasia, 5 presented with pain, 3 presented with a pelvic mass, and 3 presented with an ileocecal/appendiceal mass (one patient had both pain and mass in RLQ). Endometriosis in other pelvic sites was seen in 5/10 patients. Surgical procedures included appendectomy (4/10) and right hemicolectomy (6/10).

3.2. Pathology

The 10 cases with intestinal metaplasia had overlapping features on gross examination: 3 cases with mural or serosal nodules/masses (Fig. 1A), 3 cases with hemorrhagic foci, 2 cases with gross perforation, 2 cases grossly unremarkable, and 1 case with a cystic, myxoid lesion at the tip. One of the cases with hemorrhagic foci also displayed intussusception of the appendix. The case with the cystic, myxoid lesion (largest cyst measured 0.5 cm) at the appendiceal tip raised a concern for a mucinous neoplasm grossly (Fig. 1B)

Microscopically, all 10 cases showed extensive, transmural involvement of the appendiceal wall by endometriosis. The foci of intestinal metaplasia were submucosal in 9 cases and within the muscularis propria only in 1 case. Hybrid glands (partial intestinal and partial endometrial) were present in 9 cases (Fig. 2A–F). The endometrial epithelial cells are positive for CK7 and negative for CDX2, whereas the metaplastic intestinal epithelial cells are positive for CDX-2 and negative for CK7. The surrounding endometrial stroma is positive for estrogen receptor (ER) and CD10. Goblet cells were present in all 10 cases. A single neuroendocrine cell was present in one of the cases. Paneth cells were not identified. Other types of epithelial metaplasia were not detected in any of the cases. One of the 9 cases with hybrid intestinal and endometrial glands also showed areas of complete replacement of the endometrial glands by intestinal metaplasia with very scant, crushed stroma around the metaplastic glands (Fig. 3A–D). Due to the crush artifact, the stroma around the metasplatic glands resembled a lymphocytic infiltrate. However, immunostains (positive CD10 and ER) supported the presence of endometrial stroma. In this case, the concurrent salpingo-oophorectomy specimen was also involved by endometriosis. This finding was an additional clue to the correct diagnosis in the appendix.

Stromal decidualization was seen in 3 cases, of which 2 of the women were known to be pregnant at the time of presentation. One case showed extensive stromal myxoid change with complete replacement of the endometrial glands by intestinal metaplasia and extracellular mucin deposition (Fig. 4A–B). This case was thought to represent a LAMN on gross examination. On preliminary microscopic examination of a representative slide, the mucinous change and intestinal metaplasia misled to consider a LAMN as the top differential diagnosis. However, upon additional sampling and careful

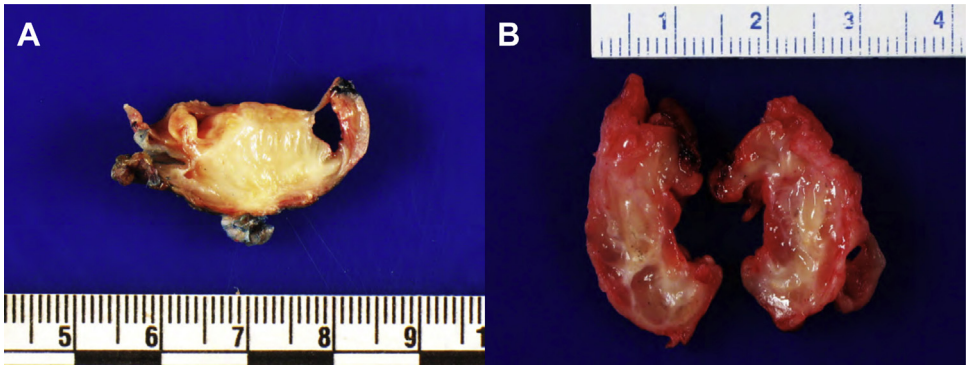

Fig. 1. A. Cut surface of the appendix showing myxoid and cystic appearance; B: Cut surface of the appendix showing myxoid and cystic appearance.