Appendiceal perforation secondary to endometriosis with intestinal metaplasia: A case report

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Abstract. Appendiceal endometriosis with intestinal metaplasia is particularly challenging to diagnose preoperatively based on clinical features. Microscopically, it can mimic malignant transformation into mucinous neoplasms of the appendix. The present study reports a case of a 47-year-old woman who presented with abdominal pain that was not related to her menstruation. The preoperative diagnosis and laparoscopic evaluation were chronic appendicitis. No mucinous or haemorrhagic secretions were present within the abdominal cavity. Pathological evaluation revealed conventional endometriosis with intestinal-type metaplasia of the epithelium. An inverse pattern of cytokeratin (CK)7, paired-box 8, estrogen receptor, CK20, caudal type homeobox transcription factor 2 and mucin 2 immunoreactivity between intestinal-type and endometrial-type endothelium was observed. Infiltration and replacement of the appendiceal wall by marked levels of acellular mucin, a lack of stromal components and a DNA mismatch repair protein profile were vital in diagnosing appendiceal endometriosis without appendiceal mucinous neoplasms (AMNs). The lesion of appendiceal endometriosis are usually superficial and small in previously reported cases but was deeply invasive in our case. A careful histopathological examination is necessary for diagnosing and distinguishing the histologic imitators of AMN.

Introduction

Endometriosis is a common disease affecting up to 15% of women of reproductive age (1). It is characterized by the growth of endometrium-like tissue outside the uterus. Endometriosis of the appendix is relatively rarely, arising in 2.8% of patients with endometriosis and in ~0.3% of appendectomy specimens (2). Appendiceal endometriosis is often asymptomatic or presents with acute or chronic abdominal pain. The definitive diagnosis is usually established following histopathological examination of the appendix after appendectomy and is easy to recognize. However, endometriosis can have unusual appearances, including metaplasia, absence of the epithelial component and destruction to the structure, and then cause diagnostic confusion. Metaplasia involving the epithelial component occurs most often in endocervical type and infrequently with intestinal-type (1,3). Intestinal metaplasia is found in 13% of cases of appendiceal endometriosis and can mimic low-grade appendiceal mucinous neoplasms (LAMNs) (1,4). Patients with appendiceal endometriosis require management by appendectomy and additional imaging evaluation is recommended to exclude any possibility of multifocal disease only. However, those with LAMN can develop intraperitoneal recurrence, or be associated with tumours of gastrointestinal tract, ovary, endometrium and breast (3), suggesting that prolonged follow-up (~10 years) or cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy is necessary (5). Therefore, despite its rarity, it is important to distinguish appendiceal endometriosis with intestinal metaplasia from intestinal mucinous neoplasms. The present study reports a case of appendiceal endometriosis clinically presenting with recurrent bouts of abdominal pain diagnosed preoperatively as chronic appendicitis. The present study was approved by the Clinic Trial Ethics Committee of Longgang District People's Hospital, Shenzhen, China (approval no. 2022013).

Case report

A 47-year-old G2P2 Cantonese woman was admitted to Longgang District People's Hospital, Shenzhen, China on December 25, 2021. She was previously healthy and asymptomatic with no family history of abdominal disease but presented with 3 months of recurrent, dull abdominal pain in the right lower quadrant of her abdomen. Associated symptoms, such as anorexia, nausea, vomiting, diarrhoea, dysuria or dysmenorrhea, were not present. She had regular menstrual cycles and was on the 14th day of her menstrual cycle. A general physical

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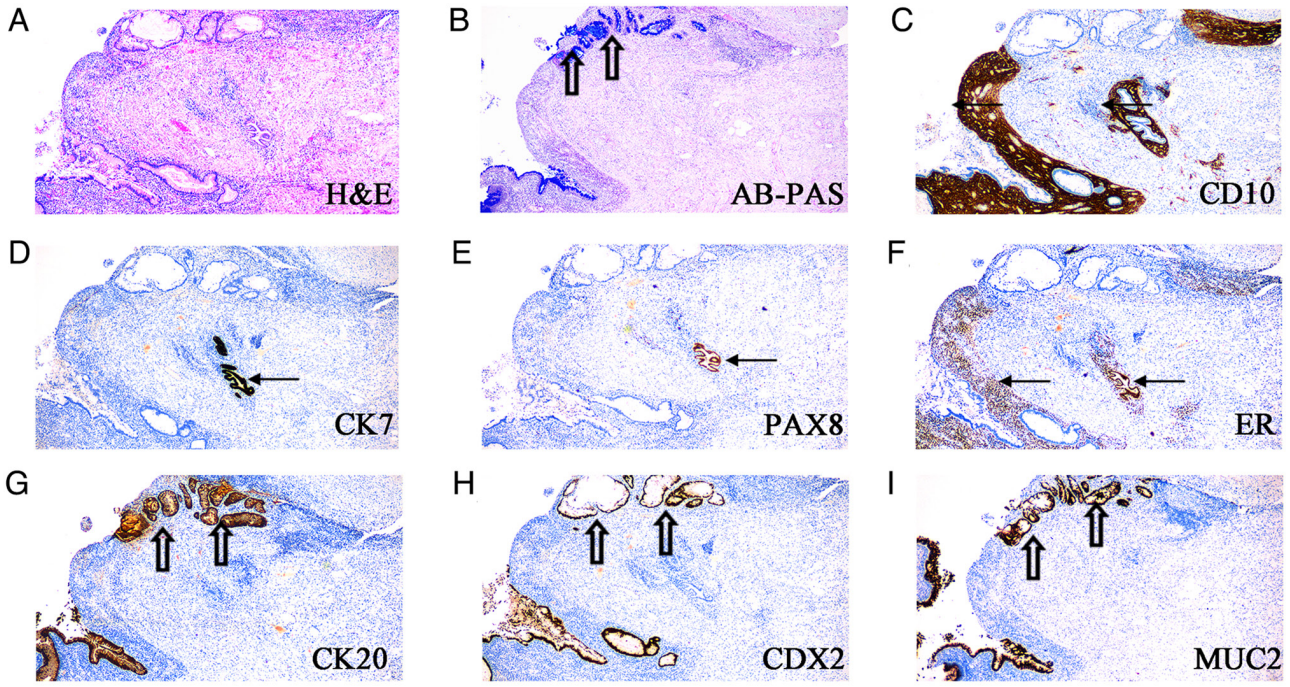

Figure 1. Endometriosis in the appendiceal wall, partially lined with glands lined by endometrial-type and intestinal-type epithelium. (A) H&E staining, (B) AB-PAS staining, immunohistological staining for (C) CD10, (D) CK7, (E) PAX8, (F) ER, (G) CK20, (H) CDX2 and (I) MUC2. Endometrial-type gland (arrow) and intestinal-type gland (hollow arrow). Magnification, x40)AB-PAS, Alcian blue-periodic acid-Schiff; CK, cytokeratin; CDX2, caudal type homeobox transcription factor 2; H&E, Hematoxylin and eosin; MUC2, mucin 2; PAX8, paired-box 8; ER, estrogen receptor. (magnification, x40).

examination did not reveal any abdominal abnormalities. A gynaecological examination was not conducted due to the absence of pelvic symptoms. Preoperative laboratory tests showed elevated white blood cell count ($16.5x10^{12}$/l) and normal C-reative protein (CRP) level (0.6 mg/dl), haemoglobin and albumin concentrations (125 and 45.4 g/l, respectively). The urine pregnancy test was negative.

Laparoscopic appendectomy was performed following a preoperative diagnosis of chronic appendicitis. Intraoperatively, the appendix measured 5x0.9 cm at the widest diameter and exhibited hyperaemia, oedema and had nearby circumferential serosal adhesions. Haemorrhaging was noticeable on the serosal surface. There were no signs of endometriosis throughout the other intra-abdominal locations in the operative field. The appendix was excised and fixed, embedded in wax, sectioned and stained with haematoxylin and eosin (H&E). Serial sections (4 μm) were also prepared for Masson's trichrome (Masson), Alcian blue-periodic acid Schiff (AB-PAS) and immunohistochemistry staining. Masson and immunohistochemistry staining were performed according to the protocols established in Department of Pathology, Jinan University School of Medicine previously (6). The following primary antibodies were used: cluster of differentiation (CD)10 (cat. no. SP67), CD34 (cat. no. BEQND/10), estrogen receptor (ER; cat. no. SP1) were purchased from Roche Diagnostics GmbH. Caudal type homeobox transcription factor 2 (CDX2; cat. no. EP25), cytokeratin 7 (CK7; cat. no. UMAB161), CK20 (cat. no. EP23), mucin 2 (MUC2; cat. no. Ccp58), α-SMA (cat. no. HUC1-1) and paired-box (PAX)8 (cat. no. OTI6H8) were purchased from OriGene Technologies, Inc. Sections were incubated in the presence of the primary antibody overnight at 4˚C after a heat-induced antigen retrieval step. Biotinylated goat anti-mouse or anti-rabbit IgG was used as the secondary antibody. Streptavidin-peroxidase system (cat. no. KIT-9901; Elivision plus; Maxim Biotech Inc.) and diaminobenzidine tetrahydrochloride substrate (DAB kit, Maxim Biotech Inc.) kits were used to visualize the staining. For AB-PAS staining, deparaffinized sections were treated with high iron diamine for 10 min followed by incubation with Alcian blue solution at room temperature for 10-20 min. Schiff reagent was poured until it fully covered the section and kept at 37˚C for 20 min and counterstained with haematoxylin at room temperature for 1 min. Images of the slides were captured using an Olympus IX51epi-fluorescence microscope (Olympus Corporation).

The postoperative course was uneventful. The patient was subjected to an ultrasonic imaging examination to search for potential deep pelvic endometriosis, but no abnormalities were found. The patient was discharged without any adjuvant treatment and denied the recurrence of abdominal pain during a regular follow-up for 12 months.

Gross evaluation revealed that the appendix was torn, with a greyish-black colour. No masses, cysts or luminal obliteration were present. Microscopic examination revealed no chronic appendicitis and few lymphoid follicles in the mucosa. However, there was an irregularly thickened wall where clusters of glands were embedded in the mucosa, muscular and serous layers. The scattered glands were composed of simple cuboidal epithelium. A densely packed, basophilic stromal component was present. All these findings suggest endometriosis.

Furthermore, the endometriosis was composed of regional intestinal-type epithelium, lined by tall mucinous cells

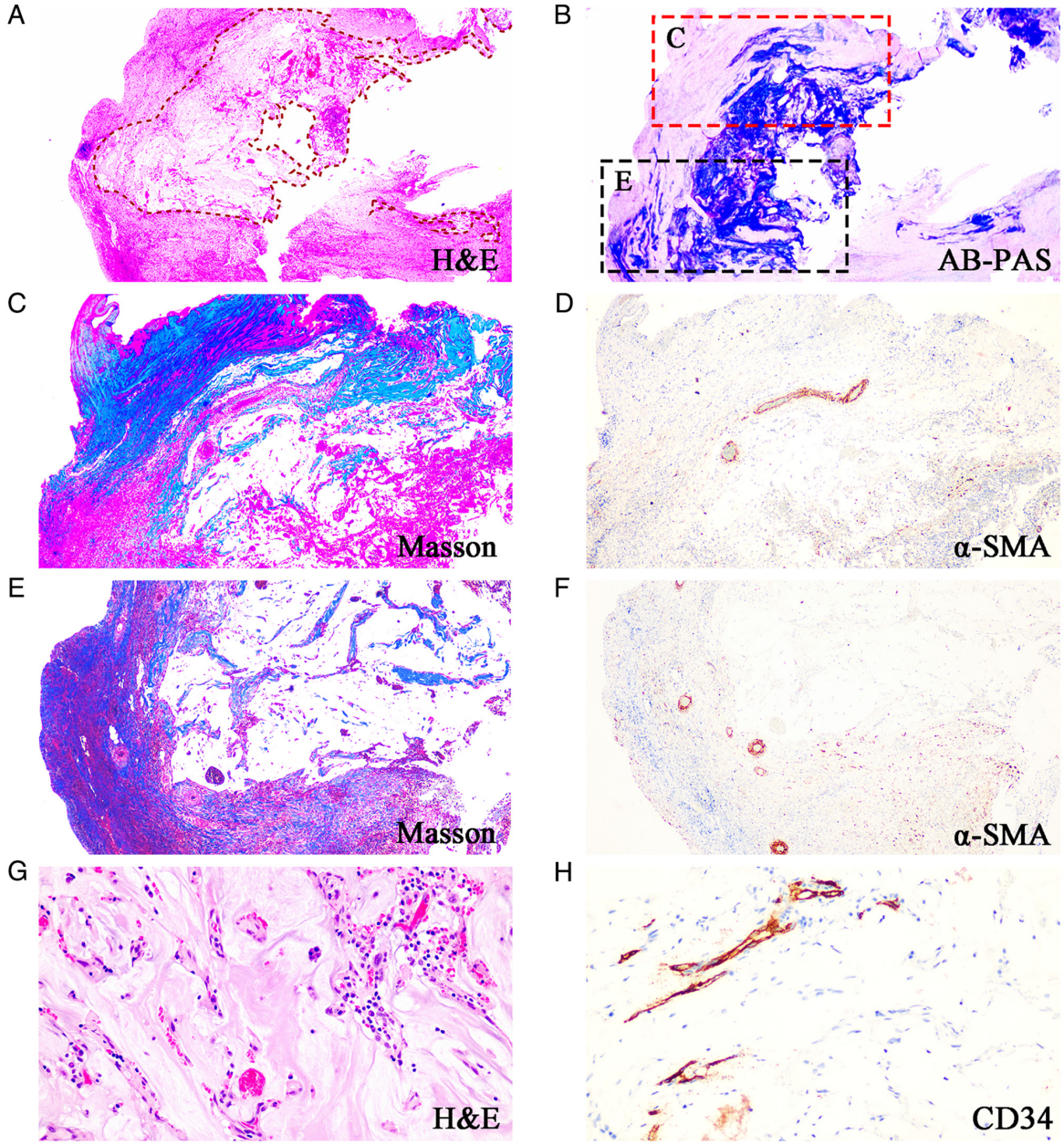

Figure 2. Endometrosis with secondary preformation and a granulation tissue response in the appendiceal wall. (A and G) H&E and (B) AB-PAS staining showed acellular mucinous infiltrative invasion in the proximal appendix. (C and E) Masson staining revealed the replacement of fibrosis. (D and F) Smooth muscles were immunohistologically stained for α-SMA. (H) Blood vessels were immunohistologically stained for CD34. Magnification: A-B, x20; C-F, x40; G and H, x200). AB-PAS, Alcian blue-periodic acid-Schiff; SMA, smooth muscle actin; CD, cluster of differentiation.

or goblet cells (Fig. 1A and B). The focal intestinal-type epithelium bordered the endometrial-type endometrium. Immunohistochemical staining analyses demonstrated an inverse staining pattern for the endometrial and intestinal epithelium. The endometrial stromal cells expressed CD10 (Fig. 1C). The simple low cuboidal epithelial cells expressed CK7, PAX8 and ER (Fig. 1D-F), consistent with Müllerian origin. The mucinous epithelium showed the following contrasting pattern: Lack of expression of CK7, PAX8 and ER and expression of CK20, CDX2 and MUC2 (Fig. 1D-I), and negative for MUC5AC and MUC6 (data not shown), consistent with intestinal origin. The intestinal-type glands were confirmed to be endometriosis as abundant clusters of CD10-positive stromal cells were found.

In some segments, mucus filled the appendix. The mucin was acellular and became deeply invasive, similar to what was affected by appendiceal mucinous neoplasm. They dissected into the appendiceal wall and there was loss of the normal architecture of the appendix, with replacement by fibrosis and with no discernible residual smooth muscle (Fig. 2A-F). Mucinous deposits are associated with a granulation tissue-like response and numerous small capillaries containing red cells were seen coursing through the mucin (Fig. 2G and H). These findings generated doubt regarding the diagnosis of a mucinous neoplasm of the appendix (2,3). However, no villous mucinous proliferation was present. The vast majority of the intestinal-type mucinous epithelium was rested in the stroma of endometriotic-type. However, stroma

of the endometriotic-type was absent and the epithelium was in direct contact with intense fibrous tissue or smooth muscle.

Discussion

Endometriosis is a benign condition characterised by the presence of ectopic endometrial epithelium and/or stroma. It is less frequently described in distant extra-abdominal sites. Although appendiceal endometriosis is rare, several studies have reported a high incidence of histopathologically proven appendiceal endometriosis in women with chronic pelvic pain (1-4). When forming the differential diagnoses, it is essential to rule out appendiceal pathologies in women with endometriosis and chronic pelvic pain. Some researchers argue that peri-appendiceal inflammation plus adhesions may suggest appendiceal endometriosis grossly (7). It is considered that fibrotic changes result from a continuous inflammatory process, which may represent chronic appendicitis or endometriosis (2). Thus, endometriosis of the appendix can mimic appendicitis and gross abnormalities are essential. However, the patient had a history of lower abdominal pain unrelated to her menstruation and showed normal findings on gross inspection, no diagnostic clues were present to cause suspicion of endometriosis before microscopic examination, thereby no other solutions contribute to predict such patients thus far.

Appendiceal endometriosis is rare and an appendiceal mucinous neoplasm (AMN) is caused secondarily to the overt growth of endometriosis (8). AMN is classified as LAMN or high-grade appendiceal mucocele neoplasm and forms following abnormal intraluminal accumulation of mucin; the amount of mucin increasing as the tumour grows. Additionally, dysplastic intestinal-type metaplasia may involve the epithelial component of endometriosis (9), which can resemble LAMN (8). Previous reports suggest that mucinous neoplasms produce abundant extracellular mucin and have clinically aggressive behaviour, infiltrating through the appendiceal wall (2,3,7). Acellular mucin has been considered as a risk for tumour recurrence and AMN staging (10). A breach in the appendix wall with acellular mucinous secretions may prompt consideration for appendiceal neoplasms, especially invasive types (5). However, in the present case, the acellular mucin lakes infiltrating the appendix wall with granulation tissue-like response and neovascularization and the presence of appendiceal perforation, are uncommon hispathological findings in endometriosis, making distinction from a LAMN difficult in the setting of abundant extracellular mucin. Immunohistochemical staining of CK7, PAX8, CD10 and ER may help diagnose an endometrial origin. Even if there is no remarkable cuff of endometrial stroma surrounding mucinous glands, lack of a recognisable intestinal primary lesion and the presence of conventional endometriosis will be helpful in diagnosis (1). Acellular mucin with neovascularization has rarely described in endometriosis, but together these data may suggest a possible role for chronic inflammation in mucin production in endometriosis.

Hapke and Bigelow (11) noted that the appendiceal pathology originates from appendicitis or luminal obstruction caused by the adhesion formed around the appendix in patients with endometriosis, as occurs with other diseases. The mucin products in in the present case appeared obstructive and dissected through the wall of the appendix, which may be related to intestinal metaplasia. Although no study, to the best of the authors' knowledge, has established the mechanism by which it occurs, endometriosis with intestinal metaplasia carries a significant risk of malignancy and is becoming increasingly recognised (7,3). Alterations in several genes are predisposing factors in the progression of endometriotic lesions to endometrial or ovarian cancer (9,12), such as KRAS mutations, Microsatellite instability and DNA mismatch repair protein deficiency (12-14). In the appendix, a more advanced investigation is required to elucidate the molecular genetic profiling involved in the intestinal metaplasia of endometriosis.

In conclusion, the present study presented a rare case of endometriosis with intestinal metaplasia. Lesions are usually superficial and small in previously reported cases but are deeply invasive, similar to that which was affected by appendiceal mucinous neoplasm in the present case. Diagnosable imaging findings, histological and immunohistochemical features facilitate a precise diagnosis for this rare case. An awareness that endometriosis with intestinal metaplasia may involve the appendix and mimic an appendiceal mucinous neoplasm is vital for preventing misdiagnosis and guiding patient management. More studies are warranted to evaluate the molecular profiles of intestinal metaplasia in appendiceal endometriosis for early detection.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MW recruited the patient and obtained specimens. PL conceived the idea, provided financial support and wrote manuscript. BH and JL analysed the data and prepared the figures. SW and PX performed the histological experiment. MW and PL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Clinic Trial Ethics Committee of Longgang District People's Hospital, Shenzhen, China (approval no. 2022013).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Chitul M, Chivu M, Chitul A, Popa I, Becheanu G, Cristian D, Grama F. Popa I, Becheanu G, Cristian D and Grama F: Appendiceal endometriosis with intestinal metaplasia mimicking appendiceal mucinous neoplasm-A case report and a concise review for the practicing pathologist. Int J Surg Pathol: Jul 14, 2022 (Epub ahead of print).
2. Klingbeil KD, Azab B and Moller MG: Low-grade appendiceal mucinous neoplasm and endometriosis of the appendix. World J Surg Oncol 15: 226, 2017.
3. Alboni C, Spanò Bascio L, Camacho Mattos L, Gallo G, Botticelli L, Cabry F, Facchinetti F and Gelmini R: Ileocecal deep infiltrating endometriosis with intestinal mucinous metaplasia and high-grade dysplasia. J Obstet Gynaecol 42: 1593-1596, 2022.
4. Vyas M, Wong S and Zhang X: Intestinal metaplasia of appendiceal endometriosis is not uncommon and may mimic appendiceal mucinous neoplasm. Pathol Res Pract 213: 39-44, 2017.
5. Valasek MA and Pai RK: An update on the diagnosis, grading, and staging of appendiceal mucinous neoplasms. Adv Anat Pathol 25: 38-60, 2018.
6. Gao L, Chen H, Liu J, Wang M, Lin F, Yang G, Lash GE and Li P: Extravillous trophoblast invasion and decidualization in cesarean scar pregnancies. Acta Obstet Gynecol Scand 101: 1120-1128, 2022.
7. Mai KT and Burns BF: Development of dysplastic mucinous epithelium from endometriosis of the appendix. Histopathology 35: 368-372, 1999.
8. Kang DW, Kim BH, Kim JM, Kim J, Chang HJ, Chang MS, Sohn JH, Cho MY, Jin SY, Chang HK, *et al*: Gastrointestinal Pathology Study Group of the Korean Society of Pathologists. Standardization of the pathologic diagnosis of appendiceal mucinous neoplasms. J Pathol Transl Med 55: 247-264, 2021.
9. Tomohiro M, Matsumoto T, Miura R, Oguri Y, Yokoi A, Tochimoto M and Saegusa M: Alterations in β-catenin, microsatellite instability, and HNF-1β levels are independently associated with ovarian endometriosis-associated tumorigenesis. Hum Pathol 89: 10-23, 2019.
10. Umetsu SE and Kakar S: Staging of appendiceal mucinous neoplasms: Challenges and recent updates. Hum Pathol 132: 65-76, 2023.
11. Hapke MR and Bigelow B: Mucocele of the appendix secondary to obstruction by endometriosis. Hum Pathol 8: 585-589, 1977.
12. Anglesio MS, Papadopoulos N, Ayhan A, Nazeran TM, Noë M, Horlings HM, Lum A, Jones S, Senz J, Seckin T, *et al*: Cancer-Associated Mutations in Endometriosis without Cancer. N Engl J Med 376: 1835-1848, 2017.
13. Yoo JY, Kim TH, Fazleabas AT, Palomino WA, Ahn SH, Tayade C, Schammel DP, Young SL, Jeong JW and Lessey BA: KRAS Activation and over-expression of SIRT1/BCL6 contributes to the pathogenesis of endometriosis and progesterone resistance. Sci Rep 7: 6765, 2017.
14. Misdraji J, Burgart LJ and Lauwers GY: Defective mismatch repair in the pathogenesis of low-grade appendiceal mucinous neoplasms and adenocarcinomas. Mod Pathol 17: 1447-1454, 2004.