

Appendiceal mucinous tumour resulting in autoamputation of the appendix: A case report and literature review

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Abstract. Appendiceal mucinous tumours are rare and can cause various complications, but to the best of our knowledge, there have been no reports of cases leading to secondary appendiceal autoamputation. Appendiceal autoamputation is the detachment of part of the appendix without surgery or other invasive interventions and is rarely observed in clinical settings. The present study reports the case of a 68-year-old male patient who was admitted to the hospital due to right lower abdominal pain and was consequently diagnosed with a periappendiceal abscess and underwent conservative anti-inflammatory drug treatment, which successfully improved the condition of the patient. Laparoscopic appendectomy was conducted 3 months later, during which the appendix was found to have partially separated; postoperative pathology revealed an appendiceal mucinous tumour. Following pathological confirmation of the diagnosis, right hemicolectomy, resection of the greater omentum and partial peritoneal resection were performed, followed by hyperthermic intraperitoneal chemotherapy in accordance with current treatment guidelines. The patient recovered well and was discharged following the operation. Considering the condition of the patient, appendiceal autoamputation was thought to be caused by the appendiceal mucinous tumour. The present case highlights the diagnostic challenges of appendiceal mucinous tumours and underscores the early standardized treatment to improve prognosis.

Introduction

Appendiceal mucinous tumours are uncommon and are detected in only 0.7-1.7% of individuals who undergo an appendectomy. The preoperative diagnosis of appendiceal myxoma is difficult and the results of imaging can only be used as a reference. The diagnosis of the disease in the vast majority of patients relies on the pathological examination (1). Appendiceal mucinous tumours are low-grade malignant tumours with a high likelihood of metastatic dissemination, and the most common type is low-grade appendiceal mucinous neoplasm, which presents as an adenomatous change in the appendix (2). The complications of appendiceal mucinous tumours vary, but to the best of our knowledge, cases resulting in autoamputation of the appendix have not been reported. Appendiceal autoamputation is defined as the separation of part of the appendix in the absence of surgical or other invasive interventions and was first documented by Judd *et al* in 1915 (3). The clinical manifestations of appendiceal mucinous tumours are typically non-specific and their imaging features exhibit marked heterogeneity, rendering preoperative diagnosis an arduous task. In most cases, a conclusive diagnosis can only be achieved through postoperative pathological examination. Over the past few decades, extensive research has been conducted on the management of appendiceal mucinous tumours, leading to the development of well-established and standardized treatment protocols (4). Ruptured appendiceal mucinous tumours are typically treated with cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) (5); CRS is defined as the surgical removal of all tumour tissue that is visible to the naked eye, as well as the exploration of potential sites of involvement, and HIPEC is a procedure whereby chemotherapeutic agents are dissolved in saline at temperatures between 42.5-43.5°C and then injected into the abdominal cavity at a rate of 400 ml/min. This is achieved through the use of an automated thermotherapy chemotherapy perfusion device, with the aim of removing both free tumour cells and mucus components. This comprehensive approach minimizes the risks of residual tumour cells and local recurrence, thereby markedly boosting the long-term survival rate of these patients and remarkably enhancing their prognosis (6).

The present case report presents a particularly unique case of appendiceal mucinous tumour. It highlights the diagnostic challenges associated with this condition, the crucial role of

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imaging and pathological examinations in its accurate diagnosis and the standardized treatment protocol. By delving into the rarity and complexity of the present case, the aim was to enhance the clinical understanding of appendiceal mucinous tumours, improving the ability of general surgeons to recognize, diagnose and manage such cases in clinical practice.

Case report

A 68-year-old male patient (body mass index, 26.1 kg/m²) presented to the Emergency Department of the Second Affiliated Hospital of Dalian Medical University (Dalian, China) in March 2023 with a chief complaint of vague abdominal discomfort in the right lower quadrant, which had been present for 10 days and had recently worsened for 1 day. Although the patient took anti-inflammatory medication prior to admission, the symptoms were not notably relieved and the patient developed a fever reaching 37.5°C. The postadmission temperature was 36.7°C, and the white blood cell (WBC) count was 11.90x10⁹/l (normal range, 4.0-10.0x10⁹/l). Physical examination revealed pressure points limited to the right lower abdomen with mild rebound pain, and CT examination revealed exudative effusive changes in the ileocecal and right iliac fossa regions with adhesions in the adjacent bowel (Fig. 1A); additionally, ultrasound revealed the presence of a periappendiceal inflammatory wrap (Fig. 1B). Based on the patient's medical history and imaging findings, the appendix was deemed to have formed complex adhesions with the surrounding tissues. Following a discussion with the patient and their family, it was determined that a complete removal of the appendix and abscess in a single surgical procedure was not feasible; consequently, a conservative treatment approach was implemented. The conservative treatment regimen formulated for the patient comprised the following measures: i) Nil per os (fasting); ii) intravenous fluid replacement; and iii) anti-inflammatory therapy, including a meloxicillin sulbactam injection, 3.75 g administered intravenously every 12 h, with a planned course of 4 days (total amount, 30 g). Ultrasound was repeated 3 days later, which revealed that the abscess had decreased in size (Fig. 1C). Following a 6-day course of treatment, the patient's body temperature returned to normal, the abdominal pain abated and no compression or rebound pain was observed upon examination. The patient was discharged from the hospital in March 2023 in stable condition (WBC count: 3.56x10⁹/l).

The patient was asked to undergo follow-up examinations, and 3 months after discharge, CT of the abdomen revealed slight thickening of the appendix and that the surrounding abscess had disappeared (Fig. 2A). The patient was readmitted to the hospital in June 2023 with the expectation of surgical treatment.

Exploration of the operative area revealed a relatively fixed and locally oozing ileocecal bowel and its mesentery, and adhesions due to a previous peripheral abscess were considered. The adherent tissues were not forcibly separated and thus the appendiceal autoamputation was discovered (Fig. 2B). The appendix was ~5 mm in diameter, the entire layer was completely dissected, the proximal end was ~3 cm long and the distal end was ~1 cm long. The two ends were connected

only by the mesentery, and the distance between the dissected points was ~1.5 cm.

The appendicular artery was visible on the medial side of the mesentery; additionally, the appendix at both ends of the dissected point exhibited robust haemato-vascular activity, with the capillaries discernible on the surface. The lumen demonstrated slight distension, and neither the proximal nor distal segments of the appendix presented any evidence of infarction, the dissected surfaces were entirely sealed. As there was no marked mucus component observed in the operative area, it was considered to be a site of appendicitis and therefore the appendix was removed (Fig. 2C).

The results of the pathological examination (neutral buffered formalin; 4% formaldehyde aqueous solution; 20-25°C; 6-24 h) were returned 3 days later, and indicated a low-grade mucinous tumour of the appendix (Fig. 3A and B). The mucosal layer of the appendix was thickened, with a smooth surface and no notable ulcers or cauliflower-like protrusions. The appendiceal goblet cells and mucus-secreting columnar cells were arranged in a columnar or cuboidal shape, with nuclei located at the basal region of the cells; the chromatin was uniformly distributed, nucleoli were inconspicuous, mitotic figures were rare (≤ 1 per 10 high-power fields) and no notable cytological atypia was observed. The appendiceal epithelium and lamina propria were compressed, showing thinning or even focal absence. Mucus had penetrated the glandular basement membrane and infiltrated into the muscular layer of the appendix, and a small number of lymphocytes and plasma cells were seen infiltrating the area around the serosal layer. The aforementioned pathological manifestations are consistent with the pathological characteristics of low-grade appendiceal myxoma (7).

Following confirmation of the diagnosis, right hemicolectomy, resection of the greater omentum and partial peritoneal resection were performed in July 2023 in accordance with established treatment guidelines (8). Additionally, HIPEC (cisplatin 75 mg/m² for 60 min) was conducted; when HIPEC was performed, the abdominal lavage fluid was stratified upon standing, with the upper layer containing clear light red turbid mucus and the lower layer containing dark red lavage fluid (Fig. 3C).

At 10 days post-surgery, the patient gradually recovered intestinal function, as evidenced by normal defecation. The patient was subsequently discharged without any new discomfort after eating, 10 days after the surgery. Pathological examination of the appendiceal mucinous tumour revealed the absence of lesional tissue on the ileocecal side, colonic side of the dissection and peripheral circumferential margins. Additionally, no lesional tissue was observed in the peri-intestinal lymph nodes (0/16) (Fig. 4). Immunohistochemistry was performed (4% neutral buffered formalin fixative; 20-25°C for 6-24 h; paraffin-embedded 4- to 5- μ m sections), indicating cytokeratin (CK)-pan⁺, CK7⁻, CK20⁺, caudal type homeobox 2⁺, mucin (MUC2)⁺, MUC5AC⁻, paired box (PAX)-2⁻, PAX-8⁻ and Ki-67 results (Fig. 5). Primary antibody details were as follows: CK-pan mouse monoclonal antibody (7H8C4; 1:200; cat. no. EM1712-42; HUABIO), CK7 recombinant monoclonal antibody (1:2,000; cat. no. 86153-7-RR; Proteintech Group, Inc.), CK20 recombinant monoclonal antibody (1:4,000; cat. no. 82428-1-RR; Proteintech

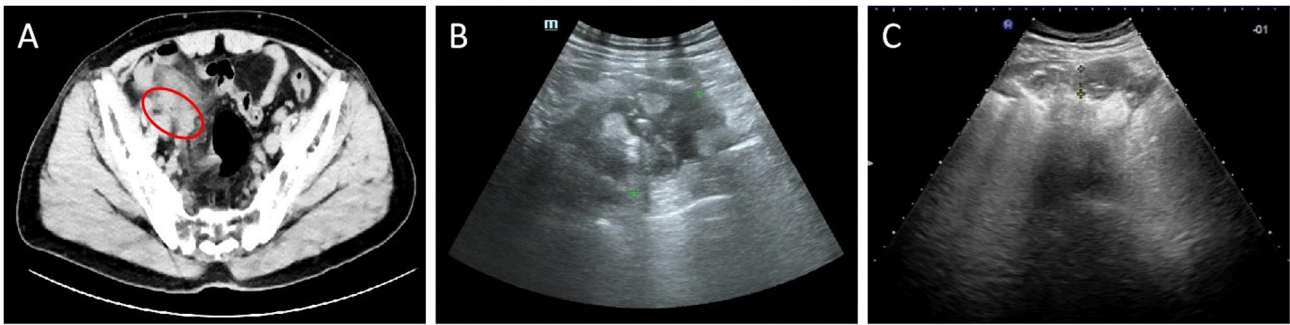


Figure 1. Abdomen CT and ultrasound examination, March 2023. (A) CT image showing oozing effusive changes in the iliac fossa area of the ileocecal region with adhesions to the adjacent bowel (red circle). (B) First ultrasound examination revealed disturbed intestinal echoes in the right lower abdominal region, mixed echoes were observed next to the iliac vessels, measuring ~6.5x5.3 cm, with tubular echoes, with a blind end on one side, and 1.6 cm at the widest point. Ultrasound suggested periappendiceal inflammatory wrapping. (C) Repeat ultrasound revealed mixed echoes in the iliac paravalses that were smaller than the previous echoes, measuring ~5.3x2.9 cm. m, m-type ultrasound mode.

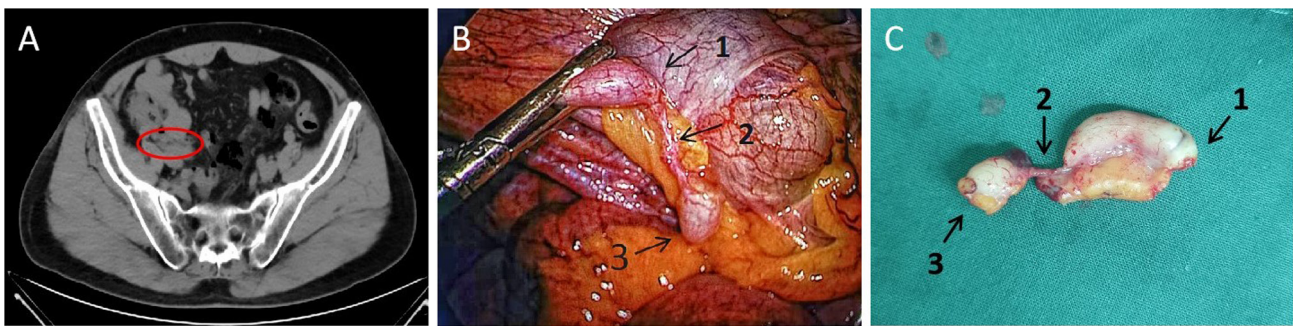


Figure 2. Abdomen CT, laparoscopic and extracorporeal appendix images. (A) CT image of the appendix, June 2023. (B) Laparoscopic view of the appendix, ~6.5 cm long (including the distance from the point of dissection) and ~5 mm in diameter. Proximal appendix (arrow 1); medial appendicular artery of the mesentery (arrow 2); distal appendix (arrow 3). (C) Gross specimen of the resected appendix. Proximal appendix (arrow 1); appendicular artery (arrow 2); distal appendix (arrow 3).

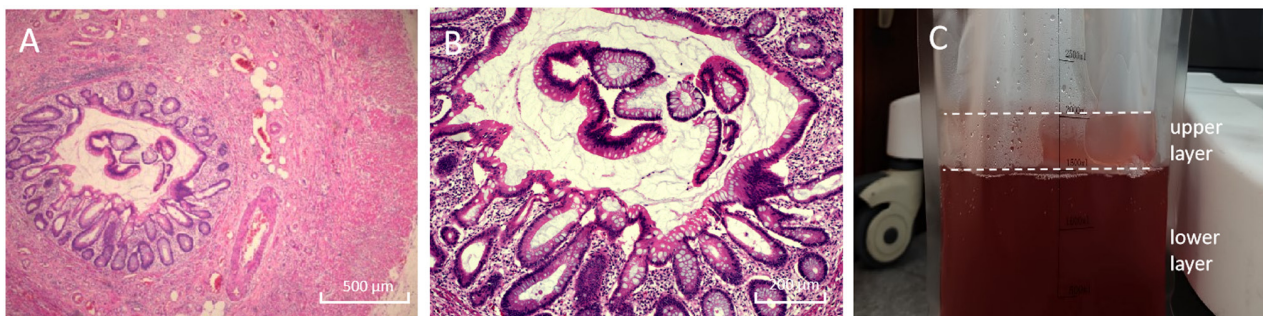


Figure 3. Microscopic pathology slides, images of peritoneal lavage fluid and resected intestinal tubes. (A and B) Haematoxylin and eosin demonstrating the disappearance of the lamina propria of the appendiceal mucosa, mucosal epithelial hyperplasia and the absence of mucus components and epithelial cells in the muscular and plasma layers were consistent with a low-grade appendiceal mucinous tumour at magnifications of (A) x4 and (B) x10. (C) Layering of the peritoneal lavage fluid; clear light red turbid mucus in the upper layer and dark red lavage fluid in the lower layer.

Group, Inc.), CDX2 recombinant monoclonal antibody (1:1,000; cat. no. 82659-1-RR; Proteintech Group, Inc.), MUC2 polyclonal antibody (1:2,000; cat. no. 27675-1-AP; Proteintech Group, Inc.), MUC5AC polyclonal antibody (1:500; cat. no. 20725-1-AP; Proteintech Group, Inc.), PAX2 polyclonal antibody (1:1,000; cat. no. 29307-1-AP; Proteintech Group, Inc.), PAX8 polyclonal antibody (1:800; cat. no. 10336-1-AP; Proteintech Group, Inc.) and Ki-67 polyclonal antibody (1:4,000; cat. no. 27309-1-AP; Proteintech Group, Inc.). Primary antibodies were incubated at 4°C for

12 h. Secondary antibody details were as follows: Multi-rAb® Polymer HRP-Goat Anti-Rabbit Recombinant Secondary Antibody (H+L) (ready-to-use; cat. no. RGAR011; Proteintech Group, Inc.), Multi-rAb™ Polymer HRP-Goat Anti-Mouse Recombinant Secondary Antibody (H+L) (ready-to-use; cat. no. RGAM011; Proteintech Group, Inc.). The secondary antibodies were incubated at room temperature for 30 min.

The patient underwent a total of three follow-up reexaminations from July 2023 to June 2024, mainly including blood biochemical and CT examinations. The 1-year follow-up after

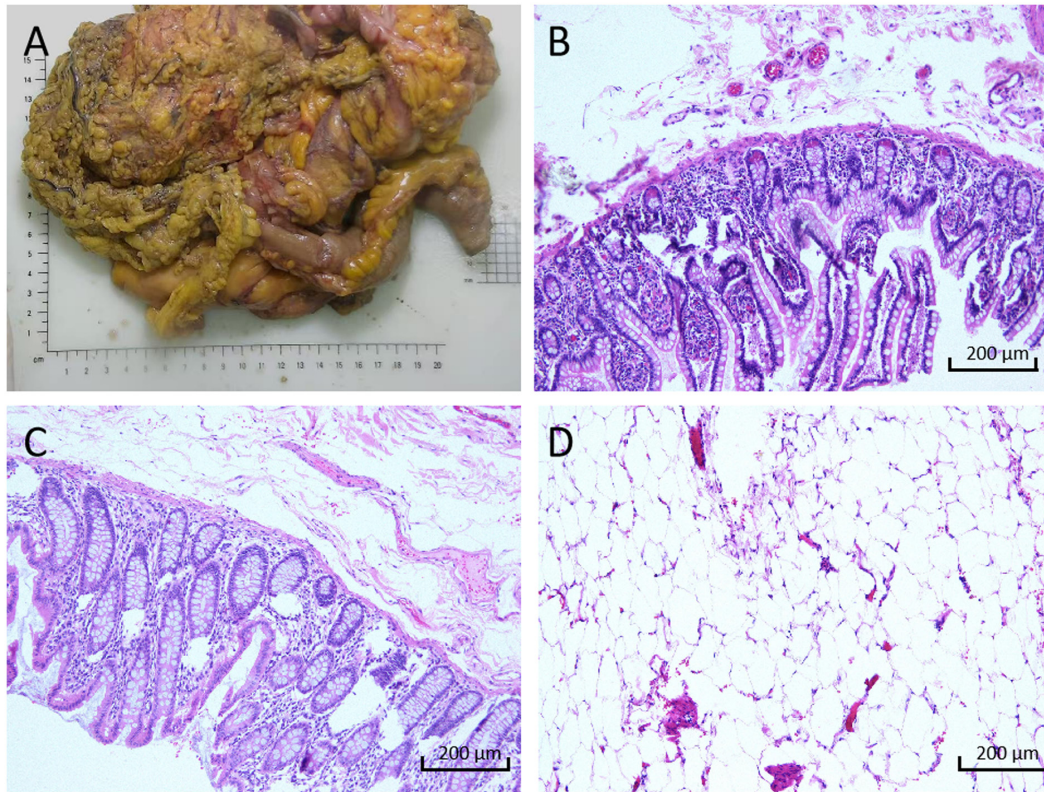


Figure 4. Gross specimen of the right colon and pathological sections of the intestinal margin. (A) Large specimen of the resected right hemicolon. (B) No neoplastic/diseased tissue was identified at the ileocecal resection margin. (C) No neoplastic/diseased tissue was identified at the lateral resection margin of the colon. (D) No pathological/diseased tissue was identified in the perienteric soft tissue or the surrounding adipose tissue.

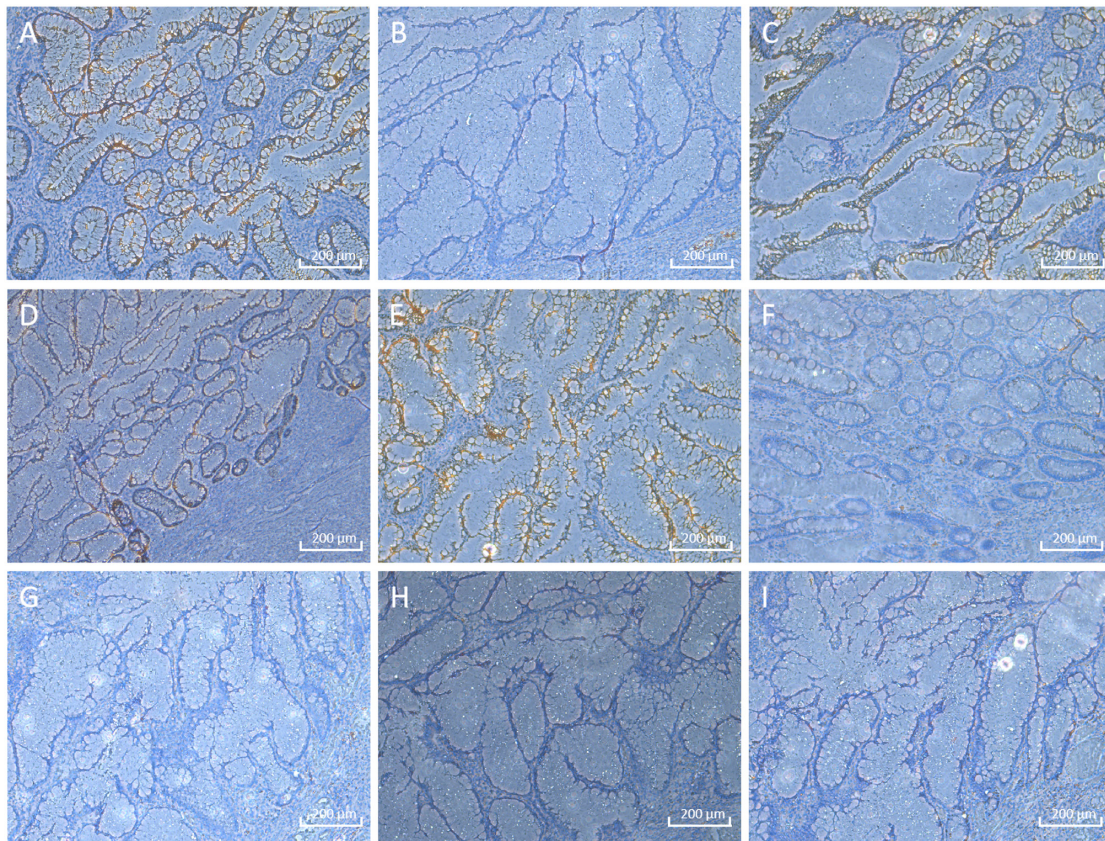


Figure 5. Immunohistochemical markers in the removed appendix tissue. (A) CKpan positivity; (B) CK7 negativity; (C) CK20 positivity; (D) caudal type homeobox 2 positivity; (E) MUC2 positivity; (F) MUC5AC negativity; (G) PAX-2 negativity; (H) PAX-8 negativity; and (I) Ki-67 negativity. CK, cytokeratin; PAX, paired box; MUC, mucin.

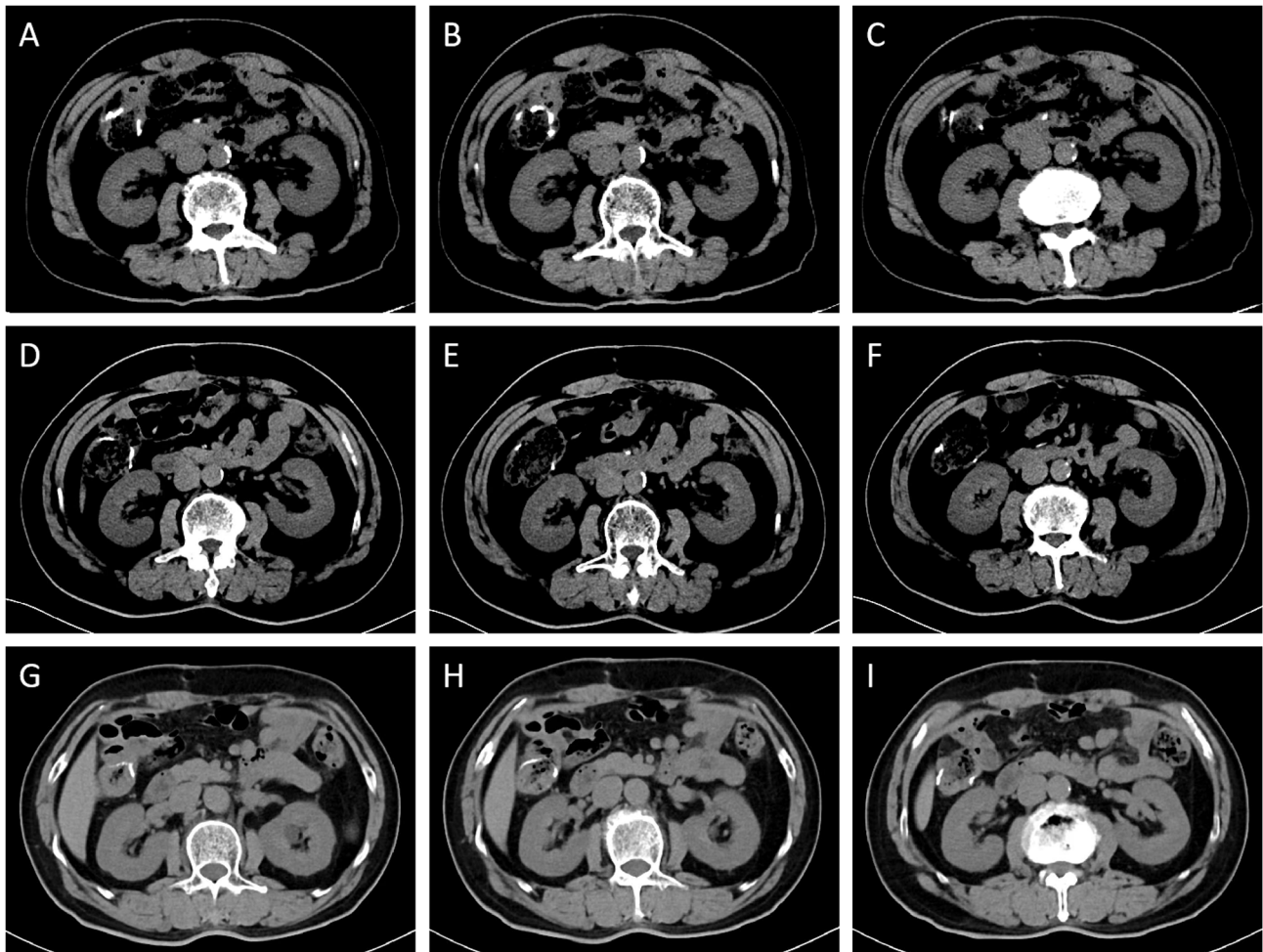


Figure 6. CT examination results of the 3 patients within 1 year of the operation did not reveal any imaging signs of disease progression or recurrence. The highlighted linear shadows in the images represent the nails of the intestinal stapler. Continuous CT images show the conditions around the intestinal anastomosis. (A-C) The CT examination performed in August 2023. (D-F) The CT examination performed in February 2024. (G-I) The CT examination performed in June 2024.

the right hemicolectomy indicated that the patient had achieved satisfactory postoperative recovery. Follow-up evaluation demonstrated the absence of clinical symptoms (such as abdominal discomfort and gastrointestinal dysfunction); physical examination revealed normal abdominal signs, including negative tenderness, no palpable masses, absent rebound tenderness and normal bowel sounds; laboratory tests showed no abnormal findings: CEA, 0.97 ng/ml (normal range, <5.0 ng/ml); CA125, 14.53 U/ml (normal range <25 U/ml); CA19-9: consistently <1.20 U/ml (normal range, <37 U/ml); and serial CT imaging revealed no evidence of disease progression or recurrence (Fig. 6). A regular follow-up examination will be performed every year in the future.

Discussion

In the present case report, a rare case of appendiceal autoamputation due to an appendiceal mucinous tumour was reported; the appendix was dissected into two parts, with good haematology at both ends. An appendiceal mucocele is challenging to diagnose preoperatively, and initially, it was assumed that the appendix had autoamputated as a result of inflammation, so an appendectomy was performed; however,

the results of the postoperative pathological examination revealed a diagnosis of appendiceal mucocele. The most common presentation of an appendiceal mucinous tumour is acute appendicitis combined with perforation. This may present with numerous symptoms, including abdominal pain (which may be located in the periumbilical area or extensive abdomen and may progressively migrate to the right lower abdomen), abdominal distension, an abdominal mass and bloody stool (4). Most patients present with atypical clinical manifestations; some individuals present with lower back pain and ileocecal intestinal obstruction (9-11). Appendiceal mucinous tumours are diagnosed on the basis of imaging data and pathological findings. CT allows for straightforward, rapid assessment of abdominal organs, but diagnosing appendiceal mucinous tumours on the basis of CT findings alone is challenging owing to the variable, ambiguous and nonspecific presentation of these tumours on CT scans. Appendiceal mucinous tumour should be considered when encountering a focal well-defined cystic mass with slightly higher than water attenuation, thickened cystic wall with ring mural enhancement and a characteristic progressive contrast enhancement on CT imaging (7). Consequently, a definitive diagnosis is often made on the basis of incidental intraoperative findings

and postoperative pathology. Intraoperative visualisation of mucus draining from the appendix or intra-abdominal findings of a distinct mucus component aids in the pathological diagnosis of an appendiceal mucocele, as do microscopic observation of villous or flat mucinous epithelial hyperplasia with low-grade isoforms and a mucin component (1,7). The immunohistochemical results were as follows: CK20-, MUC2- and MUC5AC-positive, and PAX-2- and PAX-8-negative, mostly suggestive of a diagnosis of an appendiceal mucinous tumour (12,13). The immunohistochemical results were largely consistent with the typical immunophenotypic characteristics of appendiceal myxoma, which provides objective evidence for confirming the pathological diagnosis. In addition, the immunohistochemical results further provide a basis for the differential diagnosis of this disease, as follows: i) CK-pan positivity excludes non-epithelial neoplasms, such as carcinoid tumours, lymphomas and sarcomas (14); ii) CDX2 positivity rules out the possibility of primary pancreatic myxoma (15); iii) Ki-67 negativity is consistent with the biological behaviours of low-grade tumours, supporting the exclusion of high-grade malignant tumours (16); and iv) PAX-2 and PAX-8 negativity eliminated the possibility of metastatic tumours originating from the genitourinary system or thyroid (17).

Rupture of an appendiceal mucinous tumour can result in a variety of complications, but to the best of our knowledge, cases leading to appendiceal autoamputation have not been reported. Autoamputation of the appendix has been documented in cases of appendiceal mucous cysts, gangrenous appendicitis, chronic pelvic abscesses and blunt abdominal injury (18-22). The aforementioned cases were identified as intraoperative autoamputation of the appendix, and the underlying causes and clinical manifestations of these occurrences exhibited notable differences (including abdominal pain, calcified masses, fever and free gas in the abdominal cavity).

The underlying aetiological mechanism of appendiceal autoamputation resulting from the rupture of an appendiceal mucinous tumour is the transformation of appendiceal cup cells into tumour cells, which maintain the expression of mucin throughout the process of proliferation, leading to the accumulation of mucus in the appendiceal lumen (23). As allometric tension increased, the likelihood of appendiceal rupture and perforation increased concomitantly. Owing to the absence of cell surface adhesion factors, appendiceal mucous tumour cells are capable of traversing the abdominal cavity and continuing to produce mucus (24). A clinical study showed that ~20% of patients with appendiceal mucinous tumours experienced appendiceal rupture or perforation, resulting in the formation of a peritoneal pseudomucinous tumour (PMP) (25). The 3-, 5- and 10-year survival rates for patients who develop PMPs are 100, 86 and 45%, respectively (26).

A review of the literature and relevant case material revealed that an appendiceal mucocele can be caused by chronic inflammation over a long period, which was discussed in the context of the past medical history of the patient in the present case. The current patient initially presented with a peri-appendiceal abscess secondary to appendicitis, and following anti-inflammatory and other symptomatic treatments, the inflammation subsided and the abscess was absorbed; however, the appendiceal inflammation was not resolved. After a prolonged period of chronic inflammatory stimulation,

the appendiceal cup cells undergo tumour transformation, resulting in the formation of an appendiceal mucocele, and the mucus produced by the tumour cells accumulates within the appendiceal lumen. In the presence of bacterial growth and infection, the appendix becomes gangrenous and the entire layer of the appendix undergoes necrosis. Autoamputation of the appendix occurs, and the fractured surface of the lumen closes after the expulsion of necrotic material and mucus (27).

Treatment options for appendiceal mucinous tumours have been progressively developed over the years, leading to more standardized systemic treatment protocols currently in place. For low-grade appendiceal mucinous tumours confined to the appendix, the recommended treatment is right hemicolectomy, but for patients whose appendix has ruptured secondary to PMP, CRS combined with HIPEC (28,29), a protocol first proposed by Spratt *et al* (30) in 1980, is recommended. According to the guidelines, in the present study, a right hemicolectomy, resection of the greater omentum and partial peritoneal resection were performed and the surrounding tissues and organs were cleared to minimise the risk of missing small lesions (31,32). Surgery allows extensive removal of solid tumour tissue but is limited in terms of addressing free tumour cells and their mucus secretion; therefore, in the present study, HIPEC was used to compensate for the lack of free tumour cells and the mucus clearance ability of CRS (33). HIPEC kills tumour cells through the following processes (34-36): i) Increasing the concentration of local chemotherapy and enhancing the direct cytotoxic effect of chemotherapy drugs; ii) causing microvascular embolism in the tumour tissue, resulting in tissue ischaemia and necrosis; iii) activating lysosomes to destroy the cell structure to directly kill tumour cells in the S and M phases of the cell cycle; and iv) destroying the membrane proteins of tumour cells at the molecular level, interfering with the synthesis process of DNA, RNA and proteins.

The CRS + HIPEC regimen combines the advantages of surgical resection, local chemotherapy, hyperthermia and abdominal lavage (37-40). After years of investigation and research, CRS combined with HIPEC has been identified as the optimal treatment option for patients with appendiceal mucinous tumours combined with PMP (41). A follow-up analysis of 512 patients with appendiceal mucinous tumours secondary to PMP who underwent CRS combined with HIPEC was performed. Among these patients, ~25% experienced recurrence, 375 were recurrence-free, 35 underwent reoperation and 102 experienced recurrence but did not undergo surgery. The 5-year survival rates were 90.9, 79.0 and 64.5%, respectively (42).

In conclusion, the present case report describes a rare case of an appendiceal mucinous tumour leading to autoamputation of the appendix. The present report presents a detailed analysis of the mechanism underlying the development of appendiceal mucinous tumours, accompanied by a concise overview of the literature on this subject. In addition, diagnosing appendiceal mucinous tumours preoperatively is challenging, with the specificity of the most commonly used imaging tests being suboptimal. It is therefore recommended that full exploration of the abdominal cavity and intraoperative frozen pathology is conducted when the abdominal cavity is clear and the risk of collateral injuries is low. This will facilitate an early definitive diagnosis and standardise treatment, thus reducing recurrence rates and prolonging survival.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

The present study was conceptualised by all authors. CW and YuL wrote the manuscript and collected the data. CW, YuL, ZC and SN designed and performed the analysis. YaL, BLi, Blu and XH contributed to the acquisition and interpretation of data. All authors have read and approved the final version of the manuscript. CW and YuL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of the Declaration of Helsinki, and ethical review and approval was waived for the single case report (Ethics Office, the Second Affiliated Hospital of Dalian Medical University, Dalian, China).

Patient consent for publication

Patient characteristics have been anonymized in compliance with ethical standards. Written informed consent was obtained from the next of kin for the publication of any associated images or patient data.

Competing interests

The authors declare that they have no competing interests.

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