Low-Grade Appendiceal Mucinous Neoplasm: Case Reports and a Review of Literature

Shintaro Maeda, Hirokazu Oshima, Kazuhiro Kojima and Norio Kikuchi
Department of Surgery, Sosa Municipal Hospital

Abstract
Background: Low-grade appendiceal mucinous neoplasm (LAMN) is rare. Since it can progress to peritoneal pseudomyxoma or mucinous carcinoma, appropriate diagnosis and therapy are needed. Three LAMN cases in various stages that presented within only one year to our hospital are presented.

Case presentation: Case 1 was a 75-year-old woman with right lower quadrant abdominal pain. She was diagnosed with a mucinous mucocele of the appendix and underwent ileocecal resection. Case 2 was a 67-year-old man diagnosed with chronic appendicitis who underwent appendectomy. Case 3 was a 75-year-old man who was found to have a tumor of the appendix on a periodic examination after gastric cancer surgery and underwent ileocecal resection. These three cases were diagnosed with LAMN, and their surgical margins were negative on pathology. None of them have had recurrence.

Conclusion: There are no therapeutic guidelines for LAMN. However, since it has malignant potential, correct diagnosis and optimal surgical therapy are needed. Since LAMN can be seen even in small hospitals, these cases are reported along with a review of the relevant literature.

Key words: Low-grade appendiceal mucinous neoplasm, Appendiceal mucocele, Peritoneal pseudomyxoma

Introduction
Low-grade appendiceal mucinous neoplasm (LAMN) is rare. Three LAMN cases at various stages that were seen within only one year in our hospital are presented.

Case Report
Case 1
A 75-year-old woman was admitted due to a 2-week history of right lower quadrant pain. Computed tomography (CT) and ultrasonography (US) showed that the appendix was 42mm × 18mm and had fluid within (Fig. 1). There was also a small amount of ascites adjacent to the appendix. On blood tests, inflammatory and tumor markers were negative. A mucinous mucocele of the appendix was diagnosed, and surgery was performed. At laparotomy, there was a tumor at the top of the appendix, covered with greater omentum. Since adjacent lymph nodes were swollen, ileocecal resection with D3 dissection was performed, taking into consideration of appendix cancer. The pathological findings showed that the tumor had moderate inflammatory cell infiltration, columnar epithelium producing mucus, and no atypical cells. It was diagnosed as LAMN.

Case 2
A 67-year-old man presented with right lower quadrant pain that was diagnosed as acute appendicitis, which resolved with conservative therapy by antibiotics. Two weeks later, he again had right lower quadrant pain and underwent closer examination. CT showed that the appendix was swollen with luminal fluid, and its wall was 8-mm thick. The wall thickness was not much more than at the first visit. Abscess formation adjacent to the appendix had improved compared to the first visit.
three cases of LAMN

(Fig. 2). On blood tests, although inflammatory markers were high (WBC 13.7 × 103 / μl, CRP 17.4 mg /dl) at his first admission, they were improved at his second visit. He was then diagnosed with chronic appendicitis and a tumor of the appendix. At laparotomy, the appendix was swollen, like a cystic tumor, with mild inflammation. So inflammation was cause of illness, ileocecal resection and lymph node dissection were thought over surgery. Appendectomy was performed along with a partial cecal resection to achieve a free margin. The No. 201 lymph nodes were slightly swollen and resected for sampling. Histopathological examination revealed that the appendiceal mucosa was desquamated due to inflammation, and there was attached mucus. The diagnosis was reported as LAMN.

**Case 3**
A 75-year-old man underwent distal gastrectomy for gastric cancer. Two years later, he underwent total gastrectomy for recurrence at the gastric remnant.
One year after the second operation, CT showed an appendiceal tumor. It enlarged and showed luminal secretion 3.5 years after the operation (Fig. 3). The tumor marker carcinoembryonic antigen (CEA) had risen to 9.7ng/ml; it had been normal before the operation for recurrence of gastric cancer. The patient was diagnosed with a mucinous mucocele of the appendix. Although, right hemicolectomy or lymph node dissection (D3) were considered, minimal surgery was chosen because of his complication. Ileocecal resection with D1 dissection was performed. The appendix was diffusely swollen, with no inflammatory changes and no lymph node swelling. Histopathological examination showed that the appendix wall had a mucinous lake and the epithelium was covered with atypical columnar epithelium with mucus. The diagnosis was reported as LAMN.

Discussion
LAMN is a rare disease. Its incidence ranges between 0.02% and 2.0% of all appendectomy specimens1-6. The most common clinical symptom is abdominal pain, reported in 27-64%1,2,7 of cases. Of the three cases above, two presented with abdominal pain. Although the reported rate of correct preoperative diagnosis has achieved 50%7, most LAMN cases are diagnosed by pathological findings during or after surgery. Thus, correct preoperative diagnosis is very difficult. However, the preoperative diagnosis directly affects the operative procedure2,8, and with the use of CT, US, barium enema examination, and colonoscopy, it can be comprehensively diagnosed. CT is the ideal useful technique for LAMN9; enhanced CT can be used to evaluate time-dependent changes (Fig. 1-3).

Since the surgical treatment of LAMN has not been established, the best approach for each case is determined in each hospital. The WHO classification of tumors of the appendix divides LAMN into adenocarcinoma, the same as mucinous adenocarcinoma, and signet ring cell carcinoma10. It is generally accepted that perforated cases have a high probability of being malignant1, and adequate timing of the surgical operation, before rupture or development to peritoneal pseudomyxoma, is very
In Stocchi’s study, with cystic tumors, symptomatic patients, especially with abdominal pain and weight loss, were more likely to have a malignant appendiceal mucocele. Cystadenomas were significantly larger than simple mucoceles, while no cyst adenoma was less than 20mm in the largest diameter. Thus, all mucoceles greater than 20mm should be excised. In most of the literature, appendectomy is considered the standard operation in unruptured benign mucoceles localized to the appendix, and right hemicolecction is recommended when there are malignant findings.

We also perform appendectomy with partial cecal resection or ileocecal resection to achieve negative margins. Taking all of this into account, our clinical pathway for LAMN is shown in Fig. 4. There has been a report of an association with CEA, but an elevated CEA was not a particular finding for mucinous cancer or peritoneal pseudomyxoma, and we regard it as a supplemental finding. There have been some reports of laparoscopic surgery for LAMN. Dhage-Ivatury et al. suggested that it was important to keep a mucocele intact during surgery. Thus, if a mucocele was visualized during laparoscopy, conversion to a midline abdominal incision was suggested. Another report suggested that every patient more than 50 years old who was diagnosed with acute appendicitis should undergo open surgery.

If there were not only inflammation but also malignant findings, extended surgery with lymph node dissection was needed for radical operation. So, it is important to explain the difficulty of diagnosis and the possibility for change of surgical method during operation.

Thus, the choice of surgical treatment should be carefully selected based on the stage or the experience of the surgical team. Even in inoperable cases, chemotherapy after reduction surgery has been reported.

The present three cases were each different at an advanced stage. Case 1 was preoperatively diagnosed as an appendix mucocele with no appendicitis on the first CT (Fig. 1), which showed lymph node swelling, and she underwent ileocecal resection with lymph node dissection. Case 2 was diagnosed as acute appendicitis, with a suspected appendix mucocele. At first, he was managed conservatively with antibiotics and achieved sufficient relief. After the inflammation subsided, the subsequent CT showed a persisting cystic lesion (Fig. 2). He then underwent appendectomy with partial cecal resection. Case 3 was the most advanced case. The decision to proceed with surgical treatment was considered carefully because of the past history of two gastric cancer operations.
and the presence of diabetes mellitus. The CT one year after gastric cancer showed cystic change of the appendix. Over three years of follow-up, the tumor grew about 30%, but he had no other symptoms indicative of the need for operation. However, the 3.5-year follow-up CT showed tumor growth with wall thickness. Surgical treatment was considered, but three abdominal operations seemed very invasive, and conservative treatment was chosen. However, after 6 months, CT showed more tumor growth, the tumor marker was elevated, and surgery was performed. On reviewing the clinical course, the appendiceal mucocele was over 20mm at 3 years after operation, and operation was indicated then (Fig. 3). Actually, the pathological findings showed a mucinous lake that extended into the serous layer, which suggested that the tumor developed into a pseudomyxoma.

In terms of the follow-up of case 3, the appendix mucocele was nearly unchanged 3 years after the first operation. In cases of cystic tumors, strict follow-up may be one of the options. Furman et al. suggested that interval appendectomy should be considered, especially in those 40 years or older, to determine the underlying cause of appendicitis. Actually, interval appendectomy may show the pathological findings of neoplasm rather than acute appendicitis. The decision to perform surgery for Case 2 was based on the re-emergence of symptoms after conservative therapy. However, if he had had no symptoms on clinical follow-up, if subsequent tests had shown findings indicating the need for operation, we would have unhesitatingly operated.

These three surgical cases were encountered within only one year at our hospital. In 2009–Jun.2017, we performed about 300 colorectal resections, of which 65 had disease of the appendix. LAMN was seen in the three cases described above (4.6%). Although these cases may have occurred by chance, such cases can be seen in small hospitals, such as ours.

In conclusion, Although LAMN is a rare disease, three cases at various stages that were seen within only one year at our hospital were reported. Though surgical treatment of LAMN is not yet established, it is important to have detailed knowledge of the diagnosis and surgical treatment of LAMN.

Conflict of interest: None.

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